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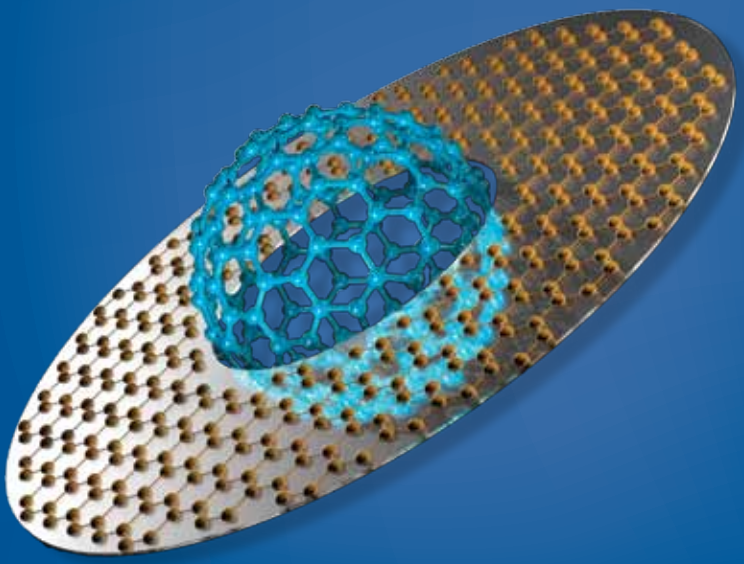
Introduction to Nanotechnology: The New Science of Small

Course Guidebook

Professors Shana Kelley and Ted Sargent
University of Toronto



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Shana Kelley, Ph.D.

Professor, Division of Biomolecular Sciences,
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Professor Shana Kelley, Ph.D. is a researcher, academic leader, and entrepreneur based in Toronto. She leads a team of 20 scientists and graduate students conducting research in the area of bionanotechnology. Professor Kelley received her B.S. degree from Seton Hall University in 1994 and her Ph.D. in Chemistry from the California Institute of Technology in 1999. She was a National Institutes of Health postdoctoral fellow at The Scripps Research Institute, where she was trained in molecular biology. Dr. Kelley began her academic career at Boston College in 2000 as an assistant professor and was promoted directly to full professor in 2006. She joined the University of Toronto that same year.

Professor Kelley has also cofounded 2 companies based on her work in biomolecular sensing. GeneOhm Sciences Inc. was a San Diego–based company acquired in 2006 by Becton Dickinson, which now markets the tests for antibiotic-resistant organisms that GeneOhm developed. Xagenic Inc. is a Toronto-based company that will commercialize a chip-based detection technology recently codeveloped by Professor Kelley and collaborator Ted Sargent, Ph.D. Professor Kelley currently serves as Chief Technology Officer of Xagenic.

Professor Kelley's research has been disseminated in leading scientific journals, including *Science*, *Nature Materials*, *Nature Nanotechnology*, and *Nature Structural and Molecular Biology*. She has published 70 original scientific papers and 10 reviews of her work, and her discoveries have been cited by other researchers more than 3000 times. Her work has been featured in *Scientific American* and *Nature Medicine* and on national television.

Dr. Kelley's work has been recognized with a variety of awards, including a 2010 E. W. R. Steacie Memorial Fellowship, an elite honor given to up to 6 Canadian scientists each year by the Natural Sciences and Engineering Research Council of Canada for research excellence. She was honored among Canada's top young leaders in 2009 and named to MIT's *Technology Review* list of the top 100 innovators in 2004. She has also received a National Science Foundation CAREER Award, a Sloan Research Fellowship, and a Camille Dreyfus Teacher-Scholar Award. ■

Ted Sargent, Ph.D.

Professor and Canada Research Chair
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Professor Ted Sargent, Ph.D. is a researcher, academic leader, and entrepreneur based in Toronto. Since 2009, Professor Sargent has served as Associate Chair for Research in The Edward S. Rogers Sr. Department of Electrical and Computer Engineering at the University of Toronto. From 2004 to 2006, he was also Visiting Professor of Nanotechnology at the Massachusetts Institute of Technology. He received his B.S. in Engineering Physics from Queen's University in 1995 and his Ph.D. in Electrical and Computer Engineering (Photonics) from the University of Toronto in 1998.

Professor Sargent leads a team of 25 scientists and graduate students conducting research in the area of nanotechnology. His research has been disseminated in *Nature*, *Science*, *Nature Materials*, *Nature Nanotechnology*, and *Nature Photonics*. His discoveries have been cited by other researchers more than 3500 times, and his work has been featured in *The Economist*, *The New York Times*, *The Wall Street Journal*, *Scientific American*, and *Nature Medicine.* He is a fellow of the American Association for the Advancement of Science and the Institute of Electrical and Electronics Engineers.

Professor Sargent is the author of *The Dance of Molecules: How Nanotechnology Is Changing Our Lives*, which has been translated into Korean, French, Italian, Spanish, and Arabic. Professor Sargent has addressed broad audiences on nanotechnology and its implications, notably at the Technology, Entertainment, Design (TED) Conference in 2007 in Monterey, California; on Parliament Hill in Ottawa; and at corporate, venture, and policy conferences around the world. In 2003, Professor Sargent was named to MIT's *Technology Review* list of top innovators under 35. He was also named to the 2005 *Scientific American* 50, an annual list "recognizing

outstanding leaders in science and technology," for his contributions to flexible infrared solar cells.

Based on inventions developed at the University of Toronto, Professor Sargent founded InVisage Technologies Inc. in 2006. The firm won *The Wall Street Journal* 2010 Technology Innovation Award in the semiconductors category for revolutionizing the capture of digital images using its patented QuantumFilm technology. InVisage is partnering for manufacture with Taiwan Semiconductor Manufacturing Company, the world's largest semiconductor foundry, and will ship its image sensors in smartphones. Professor Sargent serves as Chief Technology Officer and is a Director of InVisage. ■

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Introduction to Nanotechnology: The New Science of Small

Scope:

Nanoscience is the study of how matter behaves when it is configured on the scale of the nanometer—1 billionth of a meter. It is a field that has seen tremendous progress in recent decades. The broad advance of nanoscience has enabled nanotechnology, the application of these new ideas in areas as diverse as medicine, sustainable energy, and computing.

Atoms are the building blocks of matter; like the letters of the alphabet that compose words and sentences, atoms are combined to make molecules, such as water, H_2O, and materials, such as droplets of water, crystals of silicon, and plastics. The qualities atoms bring with them—their numbers of electrons available for bonding, the atoms' characteristic size—underpin the resultant properties of materials that emerge. Carbon atoms' 4 electrons available for bonding are at the root of diamond's tightly bound crystal lattice based on a 4-nearest-atomic-neighbor collaboration.

The rules that govern the emergence of physical properties from combinations of atoms and molecules include—but also go beyond—the classical physics of Newton. They include Einstein's and Schrodinger's quantum mechanics, wherein electrons and photons behave simultaneously as particles and as waves. Thus, electrons, though discrete and countable in number, have a spatial extent. Like the string of a guitar or the head of the tympani, the media to which electrons are tethered can be tuned in size and shape, changing their resonant frequency. The result is nanoengineered materials whose size programs the colors of light they absorb and emit.

Computing has been one of the early playgrounds for nanoscientists and nanotechnologists. The early transistors that displaced the vacuum tube were not nanometer-sized, but they did evidence key qualities, such as the smooth flow of electron waves through the pure, perfect crystalline environment of silicon. As engineers strove to increase computers' speed and sophistication, they increasingly carved and connected transistors, first on the length scale

of micrometers, and, today, of a few 10s of nanometers. Like computer chips, the lasers that generate the light waves that beam through fiber-optic cables rely on quantum nanoscale effects, as do new generations of image sensors for cameras and security inspection systems.

Medicine and biology are poised to benefit from growing dexterity at the nanoscale. DNA—the template from which proteins, organelles, cells, and ultimately, organisms are derived—is a coil of information whose double helix displays periodicity. Thus, precise interaction with the molecular basis of all life demands finesse on the nanoscale. Improved sensing of patterns, mistakes, and changes in DNA and proteins is allowing scientists to better understand the origins of disease and to catch such illnesses as cancer at the earliest stages, while they are still treatable. Nanomaterials that allow us to target specific classes of cells or certain structures within cells, such as mitochondria, allow drugs to be concentrated for maximum effect and minimized side effects. Designer nanomaterials are enabling visualization of tumor margins during surgery, allowing residual cells to be detected and surgical resection rendered accurate and complete.

Technology for sustainable energy is another field urgently needing rapid progress. Scientists are beginning to build flexible—even wearable—solar cells that efficiently capture the Sun's rays, both visible and infrared. These rainbow solar cells use nanoparticles' tunability to make optimal use of each slice of the Sun's broad spectrum. Just as importantly, nanomaterials are enabling improved means of storing energy—a critical part of turning the power of fluctuating renewable energy sources into a dependable and major source. Similarly, advances in materials engineering are allowing more efficient catalysis for the synthesis of industrial chemicals; flexible and highly efficient sources of light to replace the incandescent bulb; and, ultimately, new classes of photosynthetic analogs that enable direct solar-to-stored-fuel energy conversion.

In 1959, physicist Richard Feynman made his famous speech, "There's Plenty of Room at the Bottom." Underlying the diversity of applications in nanotechnology is a commonality of themes based on the physics and chemistry of the nanometer-length scale. For example, at the nanoscale, surface area becomes vastly larger and more important compared to

volume, and this one difference affects everything from computer chips, to mitochondria in cells, to the design of better solar panels. Common scientific principles underpin many of the advances in the field of nanotechnology. Understanding these principles puts us in a position to experience how it is possible to engineer matter—safely and with increasing control and dexterity—in order to build and use new materials having designer properties that have never existed before and, thereby, to deploy them in a vast array of exciting and important applications. ■

The Crossroads of 21st-Century Science

Lecture 1

We begin our journey into the nanoworld by trying to visualize the size of nanoparticles and looking at the advances in technology that have been achieved on this incredibly tiny scale. In the "top-down" branch of nanotechnology, matter is engineered on the nanoscale to a specific purpose; our dexterity on this length scale has enabled such innovations as computers, smartphones, and the Internet. Even more amazing is the "bottom-up" branch of the field, in which materials are engineered to self-assemble.

The Length Scale of Atoms and Molecules

- A grain of sand measures about 1 millimeter, 1/1000 of a meter; the cells in our bodies measure about 1 micrometer, 1/1,000,000 of a meter. A nanometer is 1000 times smaller than that.

- Optical microscopes are limited in their ability to resolve images by the wavelength of light, and the measure of that length is a bit smaller than a micrometer; thus, we typically can't resolve things that are smaller than that size. We need to turn to other methods to be able to visualize the world on the scale of the nanometer.

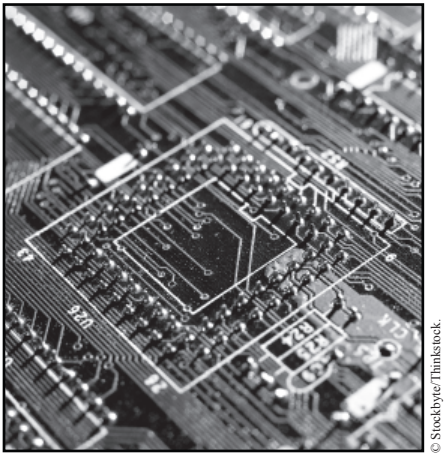
- To visualize individual atoms, we use transmission electron microscopy (TEM). A scanning tunneling microscope allows even finer resolution. Interestingly, TEM was invented around 1937 and the scanning tunneling microscope was invented around 1980, yet the two inventors shared the 1986 Nobel Prize in Physics.

What Nanoscience Enables

- We tend to think of nanoscience as a revolution that's unfolding today, but its foundations—the ability to visualize matter at the nanometer-length scale—go back many decades.

- In 1959, Richard Feynman, another Nobel Prize winner in Physics, proclaimed that there's plenty of room at the bottom. In other words, there's plenty of capability for us to increase our dexterity in manipulating matter on smaller length scales. Feynman envisioned writing the entire contents of the *Encyclopedia Britannica* on the head of a pin.

- Integrated circuits, such as those inside your computer, have billions of individual transistors on them, each of which is defined on the scale of the nanometer. It's only because we have the capability to understand the materials making up the transistor and can engineer those materials on the right length scales that we have been able to experience the computing revolution.



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Our capability to understand and engineer materials on the nanoscale has enabled the computer revolution.

- In fact, it's because of our dexterity on this length scale that we can actually sense our world. A smartphone has a GPS, temperature sensors, and proximity sensors, and all of these are connected to multiple integrated circuits, which "talk" to the Internet through wireless communications. All of these capabilities are traceable to our ability to engineer matter toward a specific purpose.

- We've taken a vast array of semiconductor technology—a vast array of building-block materials—and combined it rationally to make devices that integrate many functions.

- The Internet itself is enabled by important advances at the nano-length scale, coming, in this case, from the field of fiber optics.

Today, we're able to send trillions of bits per second of information over a single glass optical fiber cable.

- A crucial piece here was the discovery of how to make glass so pure and perfect, so lacking in defects, that we're able to ensure that light launched into one of these fiber optic cables can travel thousands of kilometers without loss of power and, thus, loss of information.

- The sources of this light must be incredibly pure and provide a single frequency that's extremely powerful and focused.

- With these semiconductor lasers, we're able to make coherent beams of light that we can launch down an optical fiber to propagate information over vast distances.

- Some of this may sound incredibly difficult to engineer, and originally, it was. But what's striking now is that many of these innovations, such as integrated circuits or fiber optic communications, have actually reduced costs.

Top-Down and Bottom-Up Nanotechnology

- We can think of these advances in the field of integrated circuit engineering—computers, lasers, the Internet, and so on—as top-down nanotechnology.

- In the top-down branch of the field, we set ourselves on a design of a device or a material, and we then make an imprint and convey that imprint using a technique called lithography. This technique is used on a massive scale—but on a very small length scale—to generate billions of identical transistors and connect them together.

- However, one of the most exciting things that's going on today in the field of nanotechnology comes from the bottom up. In this approach, we use our understanding of atoms and their interactions to engineer materials that self-assemble.

- In contrast with the top-down approach—where we have to carve up matter on the nanometer-length scale—here, we start from constituents—atoms smaller than the nanometer—and we introduce them to interact with one another such that, from the bottom up, they form new materials.

- One exciting class of new materials at the heart of nanotechnology today is quantum dots. These are semiconductor particles a few nanometers in size that invent what's called quantum size effects. Through quantum size effects, the size of the particle changes its resonance.

- When we shrink materials down to the nanometer-length scale, we also gain the capability to fit a huge amount of surface area into a finite volume. This capability is useful whenever we need a lot of surface, such as to drive chemical reactions at surfaces.
    - The catalytic converter in your car leverages having a huge surface area to convert noxious emissions into more environmentally acceptable ones.

    - Engineering materials on the nanometer-length scale gives us even greater capability to refine and control materials and chemical reactions.

- Nanoscience also gives us the ability to engineer new composite materials that have a number of properties in combination. They can be incredibly lightweight, firm, strong, or flexible.

Nanotechnology and Medicine

- If we think about the biology that underlies physiology and the anatomy of humans, we realize that we have to focus on the nanoscale. Leeuwenhoek used a simple microscope to observe red blood cells for the first time in 1684. We now know that our bodies are made up of trillions of cells, and each of these cells is about 10,000 nanometers across. Inside a cell, many structures are measured in hundreds of nanometers.

- The molecules that do all the work in our cells truly reach the nanoscale. For example, the pumps that move molecules in and out of our cells are about 10 or 20 nanometers. The proteins that keep our cells going are typically around 10 nanometers, and the DNA molecules that program our genetics measure only 2 nanometers across.

- Nanotechnology is particularly relevant to medicine because the drugs we use to treat disease are all targeted at proteins or DNA molecules. Understanding what's happening at the nanoscale allows us to make smarter drugs, such as those that can be delivered to specific sites within the body by carbon nanohorns, or nanosized drug capsules.

- The ability to work on the nanoscale means that we can see molecules more readily, which enables us to diagnose disease early, when it's most treatable. Nanoparticles can be made to act as very sensitive and specific detectors of bacteria and other cell types and can be used for this type of diagnosis. Further, nanoparticles can be activated to selectively destroy harmful cells.

- Nanomaterials can also be used to generate new types of surgical tools. Nanotweezers, for example, are able to grip particles that are close to the size of cells, enabling precise surgery to be performed.

- Another exciting area of nanomedicine research is work being done on the growth of artificial tissues and organs.
    - Scientists can engineer hard and soft materials at the nanoscale, using such techniques as lithography or self-assembly, and these nanomaterials can be used to teach cells to grow in set patterns the way they do in natural tissues.

    - It's also possible to interface these nano-trained artificial tissues with a blood supply so that they can receive oxygen and nutrients.

- Being able to work with matter at the nanoscale is a powerful way to advance a variety of important medical applications, but the distinctive properties of nanomaterials are important, as well.
    - For example, gold nanoparticles represent a promising material for disease diagnosis and treatment, both because of their small size and because of their electronic properties, which are directly tied to being at the nanoscale.

    - Regular gold, as you know, reflects yellow light. But nanoscale gold particles actually appear purple in solution—they absorb much longer wavelengths of light. This feature of gold nanoparticles arises because of a change in the electronics of gold that occurs at the nanoscale.

    - How do gold nanoparticles seek and destroy cancer cells? They can be made in a form that absorbs infrared light and converts it into cell-killing heat.

Themes of the Course

- Biology, information technology, and energy may seem to be disparate fields, but as we proceed through the course, you'll notice that a few common themes emerge.

- For example, the huge surface areas that are so important in the field of catalysis and energy have an analog in such structures as mitochondria in cells.

- Another theme that cuts across these different fields of application is commensurability. For example, with quantum dots, the sizes of electrons are matched up with the size of the "box" that will contain them, which has a powerful influence on their properties.

- These themes arise from our capacity to engineer matter, our capacity to use control and dexterity at the nanometer-length scale to build materials having designer properties that don't occur naturally.

- What's the fundamental underpinning that leads to this commonality of themes cutting across different fields of application? The answer is, essentially, a common alphabet and a common grammar.
    - Our common alphabet in nanotechnology is made up of atoms, the elements in the periodic table. The way in which these atoms assemble and form structures and the way they interact is our grammar.

    - In the next lecture, we'll spend a bit more time on this alphabet and grammar. We'll learn the common scientific principles that underpin all advances in the field of nanotechnology.

Suggested Reading

Aldersey-Williams, Hall, Sargent, and Antonelli, "Design and the Elastic Mind."

Alivisatos, "Less Is More in Medicine."

Frankel and Whitesides, *No Small Matter*.

Sargent, *The Dance of Molecules*.

Questions to Consider

1. Why do we view physics, chemistry, and biology as distinct fields of science? How could we instead view these three fields as a hierarchical stack of disciplines, each building on the others? Which would be the most fundamental, and which would be built on top of this field?

2. What are examples of devices around us—computers, mobile phones, and so on—that were enabled by key advances in science? What were the seminal conceptual advances that enabled the resulting inventions?

The Fundamental Importance of Being Nano

Lecture 2

This second lecture is our opportunity to venture into the physical principles that govern the world of the nanoscale. It's also our chance to get reacquainted with the building blocks of the nanoworld—atoms and molecules—as well as photons. We'll look at how the properties of these materials influence our experience of them and how some of the specific rules of the game are changed at the nanometer-length scale.

The Building Blocks of the Nanoworld

- We often picture an atom like a planet with electrons orbiting it. The planet is the nucleus of the atom, and it consists of a combination of protons, having positive charge, and neutrons, which are neutral.

- For nanotechnologists, the electrons are the building blocks, but the focus is on the electric and magnetic fields—the forces—rather than on the subatomic or subnuclear behaviors that are the concern of particle physics.

- What matters to nanotechnologists is the fact that the core of the nucleus has a positive charge that is attractive to electrons, which have a negative charge.

The Periodic Table

- The way in which the periodic table is formed maps to a description of shells. We think of electrons that orbit the nucleus as being able to occupy one of a number of gradually increasing energy levels. How full each of those "shells" is determines which column of the periodic table an atom resides in. The column of the periodic table, in turn, determines the personality of the atom.

- Elements in the same column often have quite similar chemical behaviors. For example, in the first column, sodium and lithium have a single electron in their outermost shells. The valance

electrons that populate that outermost shell are the key ones that relate to chemical reactivity.

- Atoms that have 1 electron available to participate in bonding represent an opportunity from the point of view of atoms having shells that are almost complete. Sodium chloride, for example, consists of sodium, with 1 valance electron, and chlorine, with 7 valance electrons.

- In this example of bonding between elements on the far left and right of the periodic table, note that the relationship is symmetric; it involves polarity. This preference for the movement of electrons in one direction or the other is called ionic bonding.

- Another kind of bonding that is much stronger is based on sharing. The kinds of atoms or elements that are most prone to this covalent bonding are those toward the middle of the periodic table, such as silicon or carbon.
  - Carbon is in group 4, which means that it has 4 electrons available to participate in bonding, and it has 4 missing in order to form a complete shell.

  - Materials in this group are sort of halfway through; they're going to form symmetric relationships with each other. For example, silicon and carbon lattices form materials that are extremely stable based on this strong covalent force.

  - The bonding of atoms with one another is one of the central tenets from which we build up materials.

- So far, in talking about these elements, we've visualized almost infinite arrays of atoms, exhibiting a systematic behavior that's common throughout the entire solid. But they're not infinite materials; eventually, a piece of silicon will have an end. At that point, we become concerned with its interface and the management of that interface.

The Classic Picture of Light

- The classic wave picture of photons of electromagnetic radiation (light) has an oscillation of an electric field and a magnetic field. If we think of a single pure color—monochromatic light—the electric field oscillates with a defined period in space and in time. That period in space is referred to as the wavelength.

- Visible light has wavelengths in the range of 400 to about 650 or 700 nanometers. It's measured in nanometers, but it's getting close to the micrometer-length scale.
  - That property of visible light is important because it turns out that a wave is difficult to condense down to a length scale that's smaller than its own wavelength.

  - Thus, the wavelength of an electromagnetic wave will determine how well it can be focused down. We can use a traditional optical microscope to see biological cells that are 10 micrometers in size, but it's much more difficult to see a virus, which can be as small as 100 nanometers in size.

  - If we're using light as a tool to carve matter or to investigate structure, such as through a microscope, we use images projected with ultraviolet light rather than visible light.

The Photoelectric Effect

- Instead of a wave picture of light, Einstein invoked a particle-like quality to light to explain the photoelectric effect. Here, light is a packet of energy.

- The photoelectric effect was observed in an experiment that involved illuminating a metal with different colors of the electromagnetic spectrum.
  - For longer wavelengths, there was essentially no emission of electrons from the metal upon photo excitation; thus, there was no photoelectric effect.

- Short wavelengths, however, produced a large number of electrons, and the intensity of that collection of electrons was in proportion with the light intensity.

- Einstein's explanation was that electrons needed to be elevated to a certain energy to escape from the metal, and that only those photons of a short enough wavelength contained sufficient individual energy.

- Einstein thought of the photons as quanta, or packets of energy, and saw a direct, inverted relationship between their wavelength and their energy.

Material Properties

- The connection between materials and light is important because many of our discussions in this course will relate to how we can shape nanomaterials in such a way as to emit light, reflect light, or convert light into an electrical form or vice versa.

- The macroscopic properties of materials, including their optical and their mechanical properties, are a manifestation of what goes on at the nanometer-length scale.
  - One way to understand this concept is to think about materials that are compositionally the same, but when you look at them in the periodic table, they have vastly different properties as a result of different confirmations, or ways in which they bind together.

  - A good example of this is carbon, the basis for diamond. As we said, carbon can bind in a covalent manner, a way in which every carbon is satisfied. Diamond, of course, is an extremely hard material, and its hardness is symmetric in all directions because this binding occurs with a kind of spherical symmetry. Thus, there's no particular plane of vulnerability for diamond.

  - Graphite is also made out of carbon, yet unlike diamond, it's soft and opaque. The explanation comes down to the nanoscale

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Both graphite and diamond are carbon based; the differences in their properties can be explained by the nanoscale structure of each material—the way in which the carbon atoms are arranged.

structure, the way in which the carbon atoms are arrayed, that is, in planar sheets stacked on top of one another.

The Quantum World

- One of the exciting regimes in nanotechnology is the exploration of how we can use nanostructured materials and the quantum effects that emerge on these length scales to control the behavior of matter and, thus, create materials having custom or designer properties.

- In this field, there's an interesting class of materials called quantum dots that take advantage of the wavelike nature of atoms. To understand this wavelike behavior, we need to look at how an electron configures itself.

- In the quantum world, we no longer think of electrons as points, the way we looked at them in the beginning of this lecture. Just as we began thinking of photons as waves but then had to consider their quantum behavior, it's also true that we're inclined to think

of electrons as particles, but they also have a spatial extent, on the scale of a couple of nanometers.

- An electron wave can be sort of a parabolic shape that's very smooth, but electrons can actually take on resonances with the materials they exist in and exhibit very complex, wavy structures.

- The visible photons we interact with as waves are measured in the hundreds of nanometers, but with electrons, we think of them as waves once we get down to the scale of a few nanometers. Quantum dots take advantage of the wavelike properties of matter.

- Consider a group of beakers filled with semiconductor particles all of the same underlying composition but glowing in different colors. The reason they exhibit different colors is that the particles are all of different sizes.
    - In the very small particles, the electron wave, which would like to be free, is confined; essentially, it's trapped in a very small box. As a result, its energy levels are elevated.

    - In the beakers that have larger nanoparticles, the electron wave is squeezed less and is able to occupy a lower energy level.

- The unavoidable wavelike nature of the electron leads to the idea of localization and the fact that we can tune material. It also leads to a curious phenomenon known as quantum tunneling.
    - To understand this phenomenon, consider how an electron would behave if it was thought of only as a particle. If an electron encountered a barrier and that barrier was of an energetic height that the electron could not climb over, then it would simply reflect back.

    - But in the world of waves, the electron isn't just a discrete particle; it has a spatial extent. Thus, when that electron arrives at the barrier, even if it doesn't have sufficient energy to overcome it, there's some probability that the electron will find itself on the far side of that structure.

- Conceiving of electrons as waves also gives us possibilities for different kinds of interactions with materials, such as partial transmission of a wave through a material and partial reflection of it.

- Quantum dots are actually another manifestation of our periodic table concept but another layer up. They allow nanotechnologists to build up a kind of periodic super-table, a new set of atom-like materials that go beyond the properties of their constituent atoms.

Suggested Reading

Callister and Rethwisch, *Materials Science and Engineering*.

Green, *Physics: Why Matter Matters!*

Nobelprize.org, "The Nobel Prize in Physics 1986."

Robinson, "Electron Microscope Inventors Share Nobel Physics Prize."

Questions to Consider

1. How is the world the same—just scaled down—when we enter the realm of the nanometer? How, on the other hand, are the rules of physics entirely transformed? What are the consequences of this new rulebook?

2. Are the colors as we see them—red, green, and blue—fundamentally distinctive from a physical standpoint, or is our definition of color a narrow and specific consequence of the particular way in which the human eye evolved? What forces prompted the human eye to evolve in this way?

From Micro to Nano—Scaling in a Digital World

Lecture 3

This lecture looks at nanotechnology through the lens of the computer revolution. We've talked from a basic point of view about electrons flowing and controlling one another. Here, we'll see that electronics and computers are really about electrons controlling other electrons and, of course, our capacity to design integrated circuits that control, program, and take advantage of that behavior. We'll also see the top-down progression of developments in electronics, from the macroscopic scale, to the microscale, to the nanoscale.

ENIAC: The First General-Purpose Computer

- The Electronic Numerical Integrator and Computer (ENIAC) was designed in World War II to enable the U.S. Army to perform rapid calculations for launching artillery. It was the first general-purpose electronic computer, meaning that it could be reprogrammed to perform other functions besides calculation.

- The way the ENIAC was programmed wasn't the way we think of programming today. It wasn't with software but with specific plugs and electrical connections.

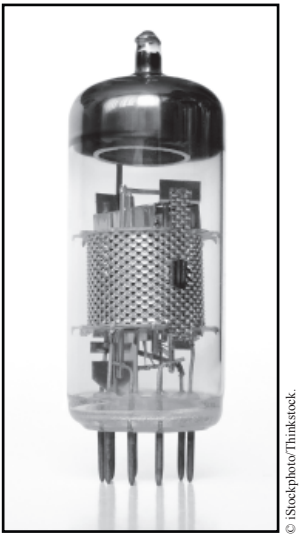
- One feature that's common to the ENIAC and computers today is the fact that they both work via electronics, that is, electrons controlling other electrons. In fact, the basis for digital computing (which uses 1s and 0s to represent information) is this: a current flowing between 2 electrodes and a 3rd electrode, either a current or a voltage, to steer the current around—to turn it on and off.

- If you can control that current flow not just with 0s and 1s—not just either on or off—but to intermediate phases, then you have the basis for analog computing, a kind of continuous electronics that allows variation. With analog electronics, if you can change the

control signal just a bit and get a large change in the current, then you have amplification.

Vacuum Tubes

- A vacuum tube looks like a light bulb, and it has something in common with a light bulb: Inside it is a vacuum. The vacuum is necessary to allow the free flow of electrons without interference from air molecules.



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The vacuum tube, the basis for early computers, offers the perfect environment for the free flow of electrons.

- If we heat up 1 of the electrodes in a vacuum tube, enough energy becomes available to result in the emission of an electron. This phenomenon is called thermionic emission. Then, with the aid of an electrical field, electrons can flow freely through the vacuum. But this is just establishing the current; we don't have electrons controlling electrons yet.

- Where the control comes in is with the 3rd electrode, which can control independently whether or not the current flows. Think of it as being in the perpendicular direction. Conceivably, we can turn on or off the flow of current using this 3rd electrode without having to invest much electrical current. That's the key to amplification: to have just a touch of a modulation on the control side that has a big impact on the flow of current.

- Of course, we can easily imagine the problems of running a computer based on something similar to a light bulb: They frequently burn out.

Transistors

- The field of transistor electronics was born of the desire to take advantage of the best properties of the vacuum tube—the free flow of electrons and control over that flow—but get beyond this reliability issue and a size issue. In the first transistors, the electronic current didn't flow through a vacuum but within a semiconductor.

- Think about a crystal of silicon. It is a perfect array of atoms, completely ordered and completely periodic. Now, think about an electron as a wave. A semiconductor uses the idea of commensurability, meaning that the wave of the electron can follow perfectly the wave of silicon atoms. The electron wave can be delocalized and ubiquitous.

- Now, without having to establish a perfect vacuum and use large tubes that have reliability issues, we are able—through the structure of semiconductors, through their crystallinity—to achieve an "everywhereness" in the electrons. That's the key element that was taken from the vacuum tube and translated into the solid state.

- From a chemical standpoint, unless we take special steps to manage the interface, silicon is not perfect at the surface of the interface. But silicon has a special property, which is that it will form what's called the native oxide (SiO_2—glass) when oxygen or water is introduced on top of it. This oxide forms a very clean interface on the surface of the silicon.

The Breadboard versus Integrated Circuits

- Of course, a single transistor is not a basis for computing. It must be connected to other transistors on a breadboard. Unfortunately, with a breadboard, you often get wires in the wrong places, which means you have to debug the circuits. This technology is also not conveniently or cost-effectively scalable. This is where the integrated circuit comes in.

- The term "monolithic integration" makes sense in this context because the innovation involves carving many transistors into

the same "rock," the crystalline piece of silicon. Typically, the transistors are just copies of one another that are connected with wiring on the 2-dimensional chip.

- The process for connecting transistors on a chip involves using a shadow mask, but this technology doesn't even get us down to the micrometer-length scale.
    - To do this, we use photolithography. Here, the mask is optically transparent in certain regions and opaque in other regions. Light projected through a lens interacts with photoresist on the wafer and forms a template for wiring or for selectively altering the properties of the silicon.

    - This lithography process enables the manufacture of incredibly scalable integrated circuits.

- One of the inevitable needs of the electronic sector is to make integrated circuits that are faster, use less power, and are more sophisticated and complex. To meet these needs and keep size under control, it's necessary to make smaller and smaller transistors.

- Of course, photolithography uses photons, which are waves, and as we said, it's impossible to confine light onto something smaller than about its own wavelength. The march forward of lithography is also the march to shorter and shorter wavelengths, from invisible, to ultraviolet, to X-ray.

- How do we ensure reliability of these circuits? As you may know, they are built in clean rooms, which minimizes the possibility that dust or particles will contaminate the transistors.
    - Today, to build a clean room costs $3 or $4 billion. For this reason, the foundry model has emerged, which allows outside organizations to pay for the use of clean room facilities to build custom circuits.

    - The foundry model is also called the fabulous model because it allows the leveraging of existing fabrication facilities.

Moore's Law

- The trend toward the smaller and smaller—what Feynman called the race to the bottom—has been described by Moore's law, an observation made by Gordon Moore, one of the founders of Intel.

- Moore said that between 1958 and 1965, there had been a doubling of what could be put onto an integrated circuit of a given size. An integrated circuit that could accommodate twice as many transistors enabled a circuit, a computer, that was twice as sophisticated and complex every 2 years.

- Moore's law can be used to describe how the integrated circuit revolution took place: We've gone from discrete elements, where we put tens of transistors onto a breadboard, to being able to put billions of transistors onto a chip. Further, it's possible to do this for costs that are measured in just a few dollars per chip.

- What we've discussed in this lecture is the precursor to the nanorevolution, but in fact, through Moore's law, we are now right up against the nanometer. We now have the capacity to use shorter wavelengths of light, through photolithography, to make transistors smaller and smaller. Inevitably, this puts us at the cusp of the nanoscale.

- In our next lecture, we'll look at what happens when we start to build transistors on the scale of the nanometer. As we continue this tremendous legacy of Moore's law, we'll find that we are doing so in a new physical regime, a regime where we encounter quantum effects.

Suggested Reading

Brock, ed., *Understanding Moore's Law*.

Ceruzzi, *A History of Modern Computing*.

Wikipedia, "History of Computing Hardware."

Questions to Consider

1. Moore's law refers to the remarkable forward march of integrated circuit/microprocessor speed, complexity, power, and cost-effectiveness over time. Can you think of examples of other fields in which a 40-year exponential growth curve has been sustained? Why is the field of the integrated circuit so distinctive in its ability to sustain such dramatic improvements over so many cycles of innovation?

2. What are the similarities and differences between vacuum tube and semiconductor transistors? Why was one down-scalable and integrable and the other not?

Leveraging the Nanometer in Computing

Lecture 4

We've seen how the success of Moore's law has allowed us to make smaller transistors and more complex integrated circuits, taking us into the nanoworld, where the rules are different. In this lecture, we'll explore how these rules become manifest, how we can manage them, and what exciting phenomena become available to us in the nanoworld. What new classes of electronic devices can we make once we gain dexterity on the scale of a nanometer?

The Workings of a Semiconductor Transistor

- A cross-section of a transistor shows 2 electrodes through which current can flow. This is called the channel, and it's exactly what it sounds like. An electron current flows through this channel, just as water might flow through a channel.

- On top is the control, referred to as the gate. The gate is used to open and close the channel through a specific mechanism. Through the application of voltage on the gate, we either attract a sea of electrons into the channel, enabling the flow of current, or repel electrons, disabling the current flow.

- The gate electrode is separated from the channel by a layer called the gate oxide. The oxide is an excellent insulator, preventing the flow of current from the gate into the channel. This means that the control requires us to expend very little current.

- In the case of silicon electronics, this oxide is the native oxide, silicon dioxide. The process by which it is grown is a natural one; the silicon wafer is simply put into a furnace. Introducing the right temperature and the right ingredients in terms of water and oxygen allows us to grow this oxide on the nanoscale.

- The native oxide is inherently disposed to passivate, or terminate, the states of the silicon that are sticking out of the substrate, the wafer. Thus, we have a natural strategy using silicon's own native oxide for passivation—for termination of these sites chemically—and for the formation of an oxide of essentially whatever thickness we desire. We just increase the temperature a bit in order to grow a more complete oxide.

Scalability

- We've spoken about scalability, a component of which is the ability to put many, many transistors on 1 integrated circuit. But in the course of scaling, we've also shrunk the transistors in the lateral dimensions in order to fit more into the same region of an integrated circuit.

- This lateral shrinking forces us to scale vertically, as well. The gate oxide must be made thinner, because it can't be too far away from where the channel is located to induce the channel. As transistors get smaller, the gate oxide must get closer to the channel.

- What happens when the gate oxide is only a couple of nanometers thick? It means we have to envision electrons as waves and think quantum mechanically.
    - If the electron is a wave and the oxide is thin on the scale of the electron's own wavelength, then that wave can be on both the left and right sides of the barrier.

    - Through the probabilities of quantum mechanics, the electron can be simultaneously on the gate electrode, where we want it, or it has some probability of ending up in the channel.

- Recall that a major advantage of the transistor model was that essentially no current flowed into the channel. Almost no current was required to switch a very large current. Through quantum tunneling, that advantage is compromised.

Nanotechnology to the Rescue

- Materials science and nanotechnology have come to the rescue on this important issue.

- Experts in these fields have discovered how to put down an insulator between the gate and the silicon that can be thicker yet can still induce the channel just as effectively. As a result, we've postponed the onset of the tunneling problem. These high-k dielectrics, these new insulating materials, are very exciting.

- Of course, in adding this insulator, we've given up the ability to simply grow the native oxide, which would then passivate everywhere across the silicon.

- There have been some interesting advances recently in putting nanometer-thin films of materials other than silicon on top of silicon. The technique is called atomic layer deposition, and it allows us to build up, layer by layer at the atomic scale, materials that we are able to interface perfectly with the silicon beneath.

- This is a great example of where by scaling down, we confronted the rules of quantum mechanics, but through innovation, we have been able to gain more runway. The longevity of the continued direct extrapolation of Moore's law has surprised a great many people.

The Advent of 3-Dimensional Devices

- Another challenge that emerges as we make transistors smaller is that some current can flow through the very short channel in what should be the off state. One solution here has been to wrap the gate electrode; the technique for making this nanoscale wrapper is atomic layer deposition.

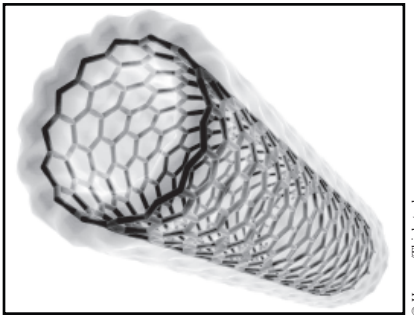
- Wrapping a gate around the channel involves etching into the silicon. When we do that, there's the possibility of creating damage below the 2-dimensional structure. That means we are starting to build silicon structures that have aspect ratios—that are tall.

- The advent of 3-dimensional devices has been viewed as very challenging, but it's starting to show some success, and it will enable us to continue to extend Moore's law, using new materials and new deposition strategies, especially at the scale of a few nanometers in length.

Carbon Nanotubes

- Carbon nanotubes are one of two fascinating materials that are showing great progress for extending the run of Moore's law. A carbon nanotube is a rolled-up piece of graphene.

- In the early 1990s, the Nobel Prize was awarded for the discovery that it was possible to make long tubes of a single atomic layer of carbon, forming a hexagonal lattice, and that these could be synthesized and purified.



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Carbon nanotubes are formed from a single atomic layer of carbon; the properties of these materials may differ depending on how they are rolled.

- Unlike a sheet of paper, which can be rolled in any direction, a sheet of graphene, with its hexagonal structure, presents fewer options for rolling. In connecting a carbon atom at the rolled end with another carbon atom, we're limited to a large but finite set of options.

- Interestingly, the properties of carbon nanotubes are different depending on the angle at which they are rolled up. For example, one can be a semiconductor and another can be a metal. This gives us a diverse material that can serve many different functions.

- Purifying carbon nanotubes—ensuring that they behave in the same way—becomes important when we try to use them to build a transistor. One way to do this is to find a technique for querying each

nanotube to identify whether it has certain properties. Research was recently published that accomplished this using DNA that would selectively stick to nanotubes differently depending on their roll-up.

- It may also be that going forward, we have to develop a new conceptual paradigm for building computers. We may have to think of ways to build computers where not every building block is absolutely identical and we don't have complete control.

- When we do that, we can start to use nanoparticles and nanomaterials that are similar but perhaps not absolutely identical. We will then need to figure out new ways of architecting integrated circuits and programming those circuits in a way that embraces the variability that occurs at the nanoscale.

Graphene

- Graphene itself, before being rolled into a carbon nanotube, has actually been a more recent star of the show in nanotechnology. The discovery and understanding of the properties of graphene was the basis for a recent Nobel Prize in Physics.

- Graphene has a rich energy landscape above it that has surprising properties for transporting electrons. In this planar structure that is only a single atomic layer thick, electrons can propagate as waves.

- The challenge here is: How do you integrate graphene, this sheet that's 0.5 nanometer thick, with a circuit, perhaps a silicon circuit? In recent years, researchers have found that they could lay down a single perfect layer of graphene onto a substrate and, thereby, start to control it.

- The rapid propagation of electrons—the fact that they just skim along at incredible velocities over this energy landscape—could be the basis for a considerable extension of Moore's law.

- Temperature presents another challenge inherent in extending Moore's law. As we crowd all these transistors together into smaller

areas, we seek to reduce the power each one uses, but nevertheless, the power density grows. Thus, there's a need for excellent thermal conductors, and graphene has shown great promise here, as well.

Revolutionary Computer Architectures

- The nanoworld presents us with properties that have not been used in digital computing. Revolutionary ways of architecting our computers may be able to exploit capabilities offered to us from the nanometer-length scale.

- A resonant tunneling diode takes advantage of current flow in the vertical direction, leveraging the flow of electrons from a top layer through to a bottom layer. This new class of devices turns to our advantage the tunneling phenomenon that was the bane of our existence in extending Moore's law to thinner gate dielectrics.

- The idea behind the resonant tunneling diode is this: We can set up an electron in a particular state on the left side of a barrier and create a state—an opportunity—for that electron to go to the right side by ensuring that there is strong coupling between the left and right only if the electron takes on a particular energy, the resonant tunneling energy.

- A resonant tunneling diode enables voltage to be applied to induce different transfer states in electrons and stable regions within them. This, in turn, allows us to create multiple-level logic in electronics. The potentials in currents are no longer just 0s and 1s but 0s, 1s, 2s, and 3s. Instead of being limited to binary logic, we can give ourselves many more options within every transistor.

- In this way, we can scale not just by making the building block smaller but by enriching the amount of information that can be stored and processed within every building block.

Suggested Reading

Bohr, Chau, Ghani, and Mistry, "The High-k Solution."

Dragoman and Dragoman, *Nanoelectronics*.

Perry, "Gordon Moore's Next Act."

Nobelprize.org, "The Nobel Prize in Physics 2010" (see "Popular Information" and "Advanced Information").

Questions to Consider

1. Could a digital computer ever be successfully built that relied on the transaction of a single electron for every computation?

2. What is the cost per transistor in one of today's billion-transistor integrated circuits? What was it in the ENIAC?

Leveraging the Nanometer in Communications

Lecture 5

In the last two lectures, we talked about how electronics has enabled computing—the processing of information at vast speeds and low cost. But these days, our computers are connected to every other computer in the world, so in this lecture, we'll look at the communications side of the computer story—the Internet. Here, we'll see how information is sent and received with high fidelity and at a very low cost per bit.

The Optical Internet

- The information-carrying backbone that resides behind our mobile communication devices is the "optical internet." This term refers to our capacity to send vast quantities of information down what we can think of as pipes—pipes that carry light.

- Light is conveyed independently through each fiber in a fiber optic bundle and modulated—turned on and off. Through that modulation and a synchronous measurement at the receiving end, we're able to convey information. The key to sending a lot of information per second is to modulate the light many times per second.

- In a cross-section of one of these "pipes," we see a light ray bouncing back and forth. This idea of bouncing is important because light tends to diffuse. If we're going to communicate information over long distances using just one of these small glass pipes, we must confine the light.
    - Optical fibers are called single-mode fibers because they have only 1 angle at which the light can bounce. The glass core and the cladding that wraps around the core are designed such that light propagates with only 1 bounce angle and, consequently, with a single velocity over very long distances.

    - That quality is engineered by creating an optical environment in which light has only two options: It can either propagate, or

it can be lost. In sending light into one of these optical fibers, only the mode in which it can propagate at a single, well-defined speed is excited.

- If the light in the optical fiber had more than one option, it would disperse, resulting in a loss of signal integrity.

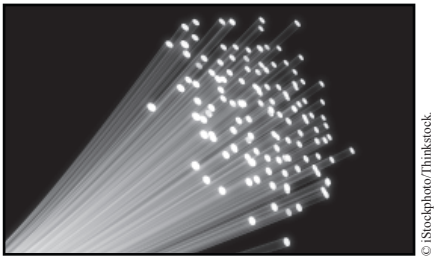
The Absorption of Light

- There are a variety of mechanisms by which light can be absorbed in any medium, one of which is "band-to-band absorption." This term refers to the idea that the available electronic state, say, in a semiconductor, cannot be successfully breached by light.
  - If a photon can come in, shine on a material, take an electron, and excite it to a higher energy, the result will be absorption.
  - Clearly, that's not what we want if we're sending information over thousands of kilometers. Optical fibers are designed to have essentially no electronic transitions available at the energies that are used to send information.
- Another way to lose light is through scattering, the phenomenon we see in clouds or fog.
  - Here, light doesn't actually transfer its energy into the particles of water that make up a cloud or fog, but having this medium that is a bit different from the air environment—a droplet of water suspended in the air—leads light to see a discontinuity, and it ends up, with some probability, being scattered in another direction.
  - You can't see through clouds or fog as a result of that scattering, and it doesn't enhance the visibility of light going down an optical fiber either.
  - The key here is smoothness. If we have an optical fiber that creates a path that isn't smooth, then we have a reason that light can scatter out of its propagating mode, rather than staying confined down the pipe.

- A certain range of wavelengths of light is particularly conducive to propagating down optical fibers without loss or scattering. At an optimal wavelength, light can propagate for more than a kilometer with almost no loss or scattering.

Properties of Light for the Optical Internet

- The light that is sent down these optical fibers must have some specific properties. First of all, it must be capable of being coupled into an optical fiber, which is only about 10 micrometers in diameter.
    - Lasers provide a beam of light having a single direction and, thus, allow coupling into the precise direction that the light will be propagating down in the optical fiber.



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The key to the realization of very low cost per bit in sending and receiving information is fiber optic communication.

    - In fact, laser beams can be tailored such that the range of acceptance angles of the optical fiber can be matched by the output of emission angles from the laser.

    - This directionality is one sense in which light from a laser is very pure and perfect.

- Another sense in which laser light is very pure is the spectral sense. Returning to our wave picture of light, we would say that it has a single wavelength, a single periodic oscillation in time and space. In the quantum picture of light, we would say that its colors have a single, well-defined energy.

Semiconductor Lasers

- How do we go about generating light with these properties? Semiconductor lasers have been developed that are extremely small

and use the semiconductor itself as the means of transferring energy from the electronic domain into the optical domain.

- These lasers rely essentially on two phenomena occurring simultaneously. The first is amplification, which refers to growing the intensity of signal—giving it more power—but retaining the underlying form of that signal. In lasers, the amplification we're referring to is amplification of light.

- The second phenomenon is resonance, which we can think of as feedback.
  - In the simplest terms, the front and back of a laser are both slightly less-than-perfect mirrors. The light generated between these mirrors is mostly trapped, but occasionally, it can escape out the front facet.

  - A photon generated in this laser cavity can be amplified into many photons, building up to a crescendo of light as they are reflected back and forth within the cavity.

  - Eventually, such an intensity of photons is built up within the laser cavity that the amount of energy being pumped in electrically to create this gain cannot amplify further; thus, we reach a steady state, an average expectation of a density of photons inside the laser cavity.

- Although they are very small, the intensities locally in the most powerful of these semiconductor lasers are amazing. Within this very small device, we've built up an incredibly high-power density using the combination of amplification and feedback.

Quantum Wells

- Inside a normal semiconductor, the energies of photons that can be produced are determined by the structure of the semiconductor, but that can be quite limiting.

- There are only certain colors that are available from a given composition of semiconductor. As we saw in discussing fiber optics, there is a very specific wavelength that is the perfect compromise to allow light to propagate for more than a kilometer with almost no loss or scattering. But it's difficult to find a semiconductor that matches that wavelength precisely.

- In quantum wells, however, we take advantage of the fact that the electron wave has a physical extent.
  - If it's a cloud, and we compress it down to 1 dimension to make a confined structure, that boosts up the energy of the electrons. We can then tune the resonance energies that this electron wave experiences, the same way one would tune a guitar.

  - By pushing these energy levels up, we're able to achieve stimulated emission, the process of gain inside the laser at exactly the wavelength that is needed.

- Through this quantum engineering—and only because of it—we're able to perfectly match the colors of light that are generated from a semiconductor with those that we desire to achieve, resulting in extremely efficient, low-energy, low-cost-per-bit communications.

- The semiconductors used here are made of such materials as gallium arsenide or indium gallium arsenide.
  - These compound semiconductors combine elements from different groups in the periodic table to achieve strong covalent bonding.

  - Introducing a third or a fourth element into the compound allows more degrees of freedom, more room to engineer the band gap of the semiconductor.

  - As a result, we're able to make materials that are much more agile, much more conducive to enabling us to choose just the right wavelength for the emission of light.

Silicon as an Optical Material

- Compound semiconductors work well in engineering discrete components, but the materials used in them are typically much more expensive than silicon. Many researchers feel strongly that if we could engineer optical materials and devices using silicon, we would be able to make the use of light in communications and, potentially, in computing much more widespread.

- As we saw during our discussions of the field of electronics, as chips are made smaller and smaller, more energy density is put into a given region of the chip. The goal is to whisk that energy away quickly so that the chip doesn't heat up, melt, or start to lose performance.

- One of the most energy-consuming factors in the operation of a chip today isn't the computing but the communications. And one of the reasons to be so interested in seeing whether electronics silicon can be integrated with optics is that we may be able to lower the energy consumption of the communications function by building it on top of a silicon chip.

- One of the elements of this work is to be able to guide light around a silicon chip in such a manner that it's not lost. Researchers have realized that silicon is actually an extremely good guide for light and can be made into highly efficient wave guides for integrated circuits.

- Another field that has attracted great excitement is plasmonics. Here, researchers are making metal particles that are spaced a defined distance from each other and allow electromagnetic waves to hop from one particle to the next. Where this is ultimately leading is the ability to convey light around a silicon integrated circuit.

- Until about 5 years ago, silicon wasn't thought of as being an active optoelectronic material; that is, it could pass light through itself, but that was about it.
    - Very recently, however, researchers have found that they can make lasers on silicon, as well as modulators that turn on and off optical signals.

- These laser and modulator technologies are now fast enough to be useful in lowering the power burden in silicon integrated circuits, but the thrust of the field now is to scale them down.

Suggested Reading

Agrawal, *Fiber-Optic Communication Systems*.

Jalali, "Silicon Photonics."

Nobelprize.org, "The Nobel Prize in Physics 2009" (see "Popular Information" and "Advanced Information, Scientific Background").

Questions to Consider

1. What properties do photons—the currency of fiber optic communications—and electrons—the currency of computing—have in common? How do they differ? Why is it important at the moment to be able to interconvert information between the electronic and the photonic domains?

2. Thinking of the price of your computer and the price of your cell phone: Which costs more, 1 unit (1 bit-flip) of computing or 1 unit (1 bit-send) of wireless communications?

Sensing the World through Nanoengineering

Lecture 6

In the last lecture, we talked about generating light—converting electronic information and power into the photonic domain. In this lecture, we're interested in the reverse process—how we transduce information about the world around us into the electronic domain for subsequent processing and communication. Light provides an incredibly rich source of information about the physical world, and here, we'll learn the role of image sensors in converting that light into the language of the digital.

Digital Cameras

- The optical module inside a cell phone has a lens that must be a certain distance from the image-sensor integrated circuit so that the image is focused onto that image sensor. There is then essentially an array of millions of pixels of photodetectors—light sensors—that are read out using this integrated circuit.

- The sensors are called CMOS integrated circuits. The use of the acronym communicates the fact that the image sensors are built using existing processes for making silicon electronics, in which there is normally no light involved. That's great news for the ability to manufacture very low-cost cameras.
    - It also puts the image sensor onto the Moore's law track. There is constant pressure to shrink the dimensions of the components of these integrated circuits and the circuits themselves.

    - Again, that's great news for fitting more megapixels into a given area, but there are some compromises that must be made when pixels are shrunk. The bottom line is that we end up having fewer photons impinge on each pixel.

The Challenges of Using Silicon

- The brilliant electronic properties of silicon have driven the emergence of the electronics industry based on it, but silicon is not a particularly strong absorber of light. That's one of the first challenges in existing image sensor approaches that use only silicon to achieve their functions.

- Another challenge comes in reading out what our pixels have "seen" in the electronic domain. For this, we need wires, but those wires get in the way of the light detector on the sensor. This problem, known as the fill factor problem, has led to deteriorating images as the size of the pixels is shrunk.

- Recently, however, light detectors have been built that can function the way silicon does, in a sense, as light absorbers that transduce photonic information into electronic currents.
    - We're able to build these detectors using a new material set, not necessarily even silicon based, involving colloidal quantum dots. These semiconductor particles are synthesized in solution so that they're just like a paint, and they can be coated onto the very top of a silicon wafer.

    - In this way, the light no longer has to pass through layers of wire to be absorbed in the silicon beneath. Instead, the sensor is brought closer to where the light impinges from.

    - Quantum dots can also be engineered to be extremely strong light absorbers. Using them is almost like putting photographic film on top of a CMOS image sensor, enabling the capture of the image on top and the reading of it using the silicon electronics below.

    - This is a return to using silicon for what it was originally intended for and what it's so effective for: the electronic function. We've built a second story on top of the silicon using nanomaterials, and this second story now reaches out and senses the light to be read by the silicon beneath.

Wavelengths beyond the Visible

- Quantum dots can be synthesized to have different sizes and, thus, different colors—different ranges of wavelengths in which they absorb or emit light.
    - The mechanism by which that occurs is the quantum size effect, wherein if we compress an electron wave down to a size even smaller than its wavelength, we push up its energy levels and turn it into a blue emitter.
    - If we make the particle of a larger size that doesn't compress the electron as much, we allow it to take on a lower energy and, as a consequence, be an absorber of lower-energy photons.

- In looking at an image of a forest fire taken with a traditional visible image sensor, we see mostly smoke. If we look at the same image taken in the infrared wavelengths, we're able to see through the smoke as a result of the interactions of different wavelengths with the particles that reside in the smoke. In other words, we're able to get more information about the scene by going to different spectral regimes in the electromagnetic spectrum.

- Quantum dot nanoparticles are not limited to only tuning over the visible spectral range. In fact, they can extend all the way to these other wavelengths that have traditionally not been the purview of low-cost silicon-based cameras.

- The infrared image of the forest fire was produced with technology using the compound semiconductors we talked about earlier, but these aren't the basis for low-cost silicon electronics. Quantum dots are now enabling the augmentation of low-cost, consumer-appropriate technology to make it capable of seeing colors that exotic semiconductors have seen in the past.

- We can also image a scene with a bullet whizzing through the air, capturing its thermal signature with an infrared camera.

Seeing Color with Digital Image Sensors

- How do we see color at all in today's digital image sensors? At the moment, the answer can be found in the arrays of optical filters that are put on top of a chip.
  - Picture a color wheel with red, green, and blue filters that can transmit those corresponding colors of light from behind a white light source. Those color wheels seek to map onto our eyes' sensitivity, where color sensing is also based on sensors that are differently attuned to red, green, and blue.

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The megapixel digital cameras in use today are incredible, but their capabilities only just scratch the surface of the information that can be garnered about the physical world using light.

  - To make a digital camera that can take color images, we overlay an array of pixels on the silicon with a matrix of red, green, and blue filters.

- This technology works, but in using it, we are throwing away quite a bit of light. Using a filter means that we are letting only certain photons through a sieve. When we do that, we're reducing the number of photons that are impinging on each of the pixels in the image sensors.

- Through their wide spectral tuning and the sharpness of their cutoffs, quantum dots and nanomaterials enable a new strategy called stacked pixels. Here, instead of using filters that throw away light, followed by sensors that sense all colors, the top sensor in a stacked pixel both detects the shorter wavelengths and filters them, passing down the green. Then, a green light–sensing layer detects

green photons and passes the red, and another layer beneath absorbs and senses the red.

Multiexciton Generation

- Nanomaterials have recently enabled researchers to see how we can use the concept of "multiexciton generation" to make more sensitive image detectors.

- To understand this term, it's important to know that normally, we expect photon detection to occur in a 1-for-1 way: 1 photon comes in, and the best case scenario is that we see 1 electron worth of information.

- In today's image sensors, we may be interested in getting down to the range where we're seeing only a few photons, a few particles of light impinging on every pixel. In that case, when we have only a few electrons, it becomes challenging to read out the information conveyed by those few electrons. We need very sensitive, low-noise circuits to do so. What if we could impart multiple electrons worth of information for every photon that comes in and, thereby, ease the burden on the circuit?

- In the phenomenon of multiexciton generation, every photon that comes in generates not 1 electron but many electrons inside the material.
    - Initially, light comes in and generates 1 excited electron, but then there's an amplification cascade. You might think of it as a billiard ball knocking into a couple of other billiard balls and generating a number of excited electrons.

    - We need a good bit of energy in this primary photon that leads to this primary excited electron generating a cascade of lower-energy electrons, but the ultimate outcome is that we have achieved multiplication from 1 photon into multiple electrons.

- In 2009, researchers found that they could make a photodetector that took advantage of this technology; as a result, they were able to see (and measure) multiple electrons worth of signal collected in a macroscopic current.

The Terahertz Spectral Regime

- One spectral regime that has been hard to access until now is the terahertz. The megahertz range is familiar to us from tuning the radios in our cars, and the gigahertz is familiar as the basis for cell phone communications. As we go to much higher frequencies than that, we get into the optical frequencies, the infrared, the visible, and beyond.

- In between the gigahertz and the optical is the terahertz regime. Until recently, the reason we had little information in the terahertz regime is that we weren't able to make efficient sources of terahertz radiation.

- However, a new class of lasers, light sources, and photodetectors has been realized based on quantum phenomena that allow the creation of terahertz photons.

- Terahertz imaging is now being used in security applications because it allows us to see through fabric and even get information on the chemical composition of material that may be concealed.

Standoff Imaging

- The field of imaging at a standoff takes advantage of the fact that we can shine a beam of light over miles and image from a distance; we can also use spectral signatures to see chemical compositional information from a distance. But sometimes, the kinds of molecules we're looking for are too subtle, too complex; there are spectral signatures that can't be discerned from miles away.

- The field of biodetection at a standoff has thus emerged, in which researchers look for very specific and subtle differences between two organisms, perhaps anthrax and something posing as anthrax.

- Scientists have come up with new ways to launch an aerosol into the region of a positive threat and have binding occur between nanoparticles (themselves containing a distinctive fingerprint) and the subject of interest; if the nanoparticles stick to the subject, they change color, and this change can be detected from long distances.

Suggested Reading

Federici, Gary, Barat, and Michalopoulou, "T-Rays vs. Terrorists."

Konstantatos and Sargent, "Nanostructured Materials for Photon Detection."

Ohta, *Smart CMOS Image Sensors and Applications*.

Questions to Consider

1. How does the resolution of photographic film compare with that of a digital camera? What limits the resolution of an imaging system, the materials on which the image is imprinted or the properties of light?

2. If we were to record information about the location of every object in the room in which you are sitting, how much memory would it take up? What if we were to record the location of every atom?

Nanomedicine—DNA and Gold Nanoparticles

Lecture 7

In the first section of the course, we learned about the impact of nanoscience and nanotechnology in such areas as computing, communications, and imaging. We're now ready to discuss nanoscience in the world of biology—a world that fundamentally operates at the nanoscale—and the applications of nanotechnology to medicine. This lecture and the next one will combine discussions of basic biological processes with nanotechnological applications.

Diagnostic Testing Using Gold Nanoparticles

- Diagnostic testing using gold nanoparticles was one of the first nano-enabled diagnostic systems to come onto the market.

- In the late 1990s, a group of researchers at Northwestern University discovered how to attach DNA molecules to gold nanoparticles. They did this by identifying a sulfur atom that was very good at sticking to gold. They then attached this atom to the end of a sequence of DNA that they synthesized. With these DNA-nanoparticle complexes, these researchers showed that they could read out mutations in very long DNA sequences from patients.

- The detection of DNA mutations has tremendous relevance to the diagnosis of genetic diseases, such as cystic fibrosis. Genetic diseases are caused by small changes in an individual's DNA that are then passed down from generation to generation.

- The gold nanoparticles were able to scan DNA molecules for these changes, and if a problem with the DNA was identified, the particles changed color. To understand how something as complicated as genetic disease can be detected with a simple color change, we need to take a closer look at three components of this diagnostic approach: the gold nanoparticle, the DNA molecule attached to the particle, and the DNA genome that is scanned.

The DNA Genome

- As we know, DNA is the molecule that stores all the information our cells need to function. It does so by programming information in a biological code. If we zoom in at the molecular level (also the nano level), we find that DNA is a double-stranded molecule, in which the 2 strands are wound around each other, forming the famous double-helical structure.

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The double helix of DNA forms as a result of attractive forces between its 4 building blocks—the bases A, G, C, and T.

- Why does this helix form, and how does it carry a code? The key feature of DNA that is relevant to both of these questions is that it contains 4 different building blocks, the DNA bases: A, G, C, and T.

- All 4 of the DNA bases have different chemical structures; these are not necessarily different kinds of atoms but atoms that are arranged differently. Thus, each base has a unique structure.

- The helical structure of DNA results from specific attractive forces between bases that dictate what partners they pair with in hydrogen bonds. The base A, for example, binds to the T, and they have 2 hydrogen bonds. The Gs bind to the Cs, and they have 3 hydrogen bonds.

- The specificity here is amazing. We can take a piece of DNA that has 100 units within it, and if we introduce the complementary sequence—in which for every A, we have a T; for every G, we have

a C; and vice versa—those 2 DNA molecules will line up perfectly, without any mistakes.

- Even more amazing than the way these bases are arrayed is what codes the genetic information required for life. The pattern of bases that is found in a DNA molecule gives the cell a full set of instructions so that it knows exactly what to do to keep itself alive and healthy.

The DNA Molecule

- In the 1940s, scientists were aware that DNA was most likely the molecule of life, and they knew that it included different amounts of the 4 units, but they didn't know what the molecule might look like.

- James Watson and Francis Crick got a start on finding the structure of the molecule using stick-and-ball models. At the same time, Rosalind Franklin and Maurice Wilkins were using X-ray diffraction to try to understand the molecule's structure.

- A major breakthrough came when Watson and Crick saw Franklin's famous Photograph 51. This was an X-ray diffraction pattern of a DNA sample. The fuzzy X in the middle of the molecule is not a direct image of DNA but the diffraction of X-rays bounced off of DNA. This pattern indicates a helical structure, and it was this information that allowed Watson and Crick to determine the structure of the DNA molecule.

- There are 6 billion bases in the DNA found in every cell. Each base takes up about 0.3 nanometers in a linear sequence. This means that for every 10 base pairs, you have about 1 nanometer of DNA; 100 base pairs give you about 10 nanometers; and so on. Stretched end to end, there are about 2 meters—more than 6 feet—of DNA in every cell! The reason we can fit all of this DNA in our cells is that it's not present in a linear form; it's condensed into tiny particles.

Gold Nanoparticles

- Patients affected with cystic fibrosis typically have mutations in a gene that dictates how well their cells can deal with salts. For example, the most common mutation causes 3 bases to be missing from a sequence that codes for a protein that is essential for cellular function. This causes mucus to accumulate in the lung, and serious bacterial infections result that interfere with breathing.

- How do gold nanoparticles sense mutations like this? As we've seen, DNA consists of 2 complementary strands in the cell. If we want to target a particular sequence of DNA to diagnose a disease that would result from mutations in that sequence, we can take a manmade strand of DNA and design it to stick to the region of the mutation; how well it sticks will tell us whether the mutation is present or not.

- In order to detect the cystic fibrosis mutations, two different types of gold nanoparticles can be made that will line up specifically with the region of mutated DNA. If the altered DNA sequence is present, the gold nanoparticles will bind to it, and when this happens, the nanoparticles will change from red to blue. It's that color change that tells us that the mutant sequence is present.

- Of course, macroscale gold—gold in its metallic state—isn't red and it doesn't change color. But when nanoscale gold is dispersed in solution, it has a very different set of properties. Its red color is related to the nanoscale size of those particles.

- The fact that nanoscale objects can have a completely different set of properties from macroscale versions is a key point that illustrates why nanomaterials have unique utility.
    - The color change that we've seen and the red color of gold nanoparticles in solution arise because of the interactions of the particles with light.

    - The fact that the oscillations of light are on about the same size scale as the nanoparticles allows a unique interaction.

- Macroscale gold doesn't interact with light; it merely reflects light. But with gold nanoparticles, we have electromagnetic waves that are dispersed on the surface of the particle, where there are highly delocalized electrons. The wavelengths of light and the waves on the surfaces of the particles interact and dictate what color the particles appear to be to the human eye.

- Gold nanoparticles that are not surrounded by water and not close to other particles appear to be red. When the nanoparticles come close to one another, they appear blue. Again, it's the same material, but it has a different distance separating it.
  - The fact that the absorption of this material becomes blue means that the particles become electronically coupled. The electrons actually start talking to one another; they know that others are there, and that perturbs the surface waves on the nanoparticles.

  - That perturbation of the surface waves gives us the color change that we see when nanoparticles line up on a strand of DNA in the presence of a disease-related mutation.

The Technology in Use

- A company that was launched out of Northwestern University developed an instrument to automate the process of using gold nanoparticles to detect genetic mutations, and the technology is now being used in hospitals across North America.

- In a testing laboratory, a technician can take a sample of blood, extract the DNA from the cells, purify it, and inject it into a cartridge that can mix it up with nanoparticles. This mixture is then put onto an array, which picks out patterns of blue spots or pink spots, allowing doctors to know what mutations are present in the sample.

- This type of testing instrument, in addition to being used for cystic fibrosis testing, can also be used to determine whether patients have mutations that make them sensitive to certain drugs. Viruses and bacteria can also be detected with the instrument.

- As mentioned earlier, this is one of the first nano-enabled diagnostic systems to come onto the market. In future lectures, we'll discuss other types of diagnostic approaches that are a little bit earlier in their development but have just as much promise.

Suggested Reading

Maddox, *Rosalind Franklin*.

Nanosphere, Inc. (corporate Web site).

NOVA, "Secret of Photo 51."

Seeman, "Nanotechnology and the Double Helix."

Vo-Dinh, ed., *Nanotechnology in Biology and Medicine*.

Watson, *The Double Helix*.

Questions to Consider

1. How does DNA transmit genetic information from one cell to another? How does this capacity relate to the ability of DNA to link nanomaterials?

2. Why is reading out DNA sequences relevant to disease diagnosis? For what diseases is this type of diagnostic approach most relevant?

Nano and Proteins—Enzymes to Cholesterol

Lecture 8

Just like DNA, which we covered in the last lecture, proteins are a major class of biomolecules that can connect biology directly with the world of nanotechnology. In this lecture, we'll look at some of the basic features of proteins and see how these features have been used to manipulate nanomaterials or how they can be made useful for applications in nanoscience and nanomedicine.

The Structure of Proteins

- Proteins are a type of cellular molecule that—unlike DNA—have a wide range of functional roles and structural motifs. They drive all the chemical reactions that occur within cells, they provide structural support to cells and tissues, and they control what molecules are allowed in and out of cells. Proteins are also the key players in the immune system; they recognize foreign cells, such as bacteria and viruses, and target them for destruction.

- Proteins are composed of amino acids, which are no more than 1 nanometer in size. The ordering of the amino acids within a protein can have a strong effect on structure. That ordering is determined by the information in DNA.

- The first glimpse of protein structures at the nanoscale came around the time that DNA's structure was first characterized. It was much harder to interpret the protein data, however, because unlike the simple double-helical structure of DNA, proteins have structures that are highly variable.
    - Consider, for example, the protein hemoglobin. This protein carries the oxygen from our lungs to other sites in the body.

    - Notice that there are curly, helical sections in the protein structure, but it's not a straight, continuous helix like DNA. There are also sections that are not helical, that are interspersed,

and these can be quite disordered. This is one of the things that made structural characterization of proteins extremely difficult.

- Another challenge was that there are 22 different amino acids that can be present within a protein, and having so many building blocks made it much more challenging to fit everything together.

- Why are the structures of proteins so variable? The answer is probably connected to the fact that they perform so many different functions within the cell. Some proteins have evolved to very specifically recognize other proteins or even DNA or other molecules; thus, their structures are designed to find and bind partners.
  - The helical sections that we find in proteins are rigid, so they're good at grabbing chemical functionalities on other molecules. This is where different amino acids come in. The ones that are good at making hydrogen bonds can reach out and make contact with other molecules.

  - The linker regions that we saw in hemoglobin are quite flexible, and they're good at allowing a protein to change its shape to give off a signal. In this way, proteins can tell a cell whether it's cold or hungry so that the cell can respond.

  - Other structural motifs that are found in proteins can provide binding pockets where chemical reactions can occur.

Proteins as Catalysts

- One of the most ubiquitous functions of proteins is the catalysis of chemical reactions. Proteins are good at making unreactive molecules do something special. They do this by binding molecules in special pockets where they can bend the molecule to put it under stress and break a bond, or they can use one of their own functionalities to cut or replace a chemical bond.

- As an example, let's consider the peroxidase enzymes, which break down peroxides, such as hydrogen peroxide.
    - On its own, hydrogen peroxide is pretty stable, but when it binds the peroxidase, it's cut in half and made very reactive. This is an important function that helps the immune system fight disease.

    - In the presence of an infectious agent—for example, a bacterial cell—the enzyme converts hydrogen peroxide into a reactive molecule that will stop the bacterium in its tracks by damaging its cell wall.

- Interestingly, the enzyme peroxidase seems to be able break down and biodegrade carbon nanotubes, which is an important discovery for drug delivery using nanotubes. This degradation process takes place from the outside layer of the nanotube and works toward the inner layers.

Antibodies

- Antibodies represent another important class of proteins. Antibodies are able to specifically recognize foreign agents in our bodies and tag those foreign agents so that they're eliminated. Most antibodies have a Y shape, with a stem and two recognition domains that are very specific sensors.

- How do these proteins recognize threats to the immune system? Our bodies have large libraries, or sets of antibodies, and every member of this set is slightly different. Once one of these antibodies finds something threatening, it gives off a signal that says it should be amplified, and many copies of it are made to ensure that an infection is cleared.

- As you know, our immune systems can sometimes turn against us. For those people who have certain food allergies, it's the immune system and antibodies that mistakenly treat a certain component of a food as a threat.

- We have also learned, however, to make our immune systems work better. We know how to vaccinate against many diseases by injecting substances that mimic infectious agents to trigger antibodies.

- We also know how to produce highly specific antibodies in large quantities so that we can exploit their binding properties for medical applications. There are several antibody-based drugs that are able to find specific proteins on the surfaces of cancer cells and selectively eliminate them just as if they were bacterial cells.

- Antibodies are a powerful tool in nanomedicine. For example, antibody–gold nanoparticle conjugates are already used as indicators in many commercially available pregnancy tests. The red lines that appear when urine is introduced onto the testing stick are formed with gold nanoparticles.
    - In these tests, an antibody that specifically binds the hormone hCG is modified with a gold nanoparticle.
    - If hCG is present, it binds to the antibody, and a large complex is formed. This complex flows along the testing stick until it reaches the test site.
    - At the site, a filter stops the large complex from flowing through and concentrates it into a line.
    - Close by, any leftover gold nanoparticles that are still present are trapped by a finer filter and used as a control (a single red line) to show that the sample was actually transported through the device.
    - In this way, the intense color and the nanoscale size of the particles are leveraged to make this type of diagnostic testing easier and more sensitive.

Passive Protein Functions

- Not all proteins have what we would consider active functions. Some of these passive functions are present to provide structure to a cell or a tissue.

- For example, collagen is a main component of connective tissue, and it represents 30% of the total protein in our bodies. It always exists as a triple-helical structure, about 1.5 nanometers wide and 300 nanometers long. These triple helices of collagen are wound into tough bundles that can be hundreds of nanometers thick, and they provide a guide that tells cells where to grow.

- Scurvy is one of a number of diseases that are related to problems with collagen. The vitamin C deficiency that causes scurvy produces defective collagen, which affects connective tissues. The gums in the mouth are particularly susceptible to this, and tooth loss was a major ramification of scurvy. The process of wound healing is also expedited by collagen, and slow healing was a major symptom of scurvy.

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As we age, the collagen in our faces and elsewhere breaks down, causing our skin to lose structure; cosmetic procedures attempt to reintroduce collagen to repair these effects.

- Collagen is an intensely studied protein because of its role in our physical appearance. The changes that appear in our skin as we age come about because of collagen breakdown. Many cosmetic procedures have been developed that attempt to reintroduce collagen to repair the effects of aging. Collagen is also an important component in types of artificial skin that are under development for treatment of burn victims.

- Collagen has been used as a model for the development of nanomaterials that can support cell growth. As mentioned earlier, collagen is oriented in fibers, and its directionality and the spacing of the fibers tell cells how to position themselves. This natural phenomenon has been mimicked with nanomaterials.
    - Researchers at MIT have produced nanoscale gratings that mimic the structure of collagen, and they have found that these gratings are effective at orienting cells.

    - It's important for cells to have directionality in order to be able to build up tissues and organs in an organized manner; thus, these types of materials have tremendous promise for artificial tissue engineering.

Proteins as Cellular Gatekeepers

- Delicate balances of different molecules must be maintained in cells, and there are proteins that sit on the surfaces of cells whose function it is to decide what should be allowed into and out of the cell.

- These proteins, called receptors, are inactive if they do not have anything bound, but once they bind something, they trigger an amazing chain of events, causing the cell to make pockets in its outer membrane that allow the receptor to bring materials into the cell.

- This type of process plays an important role in how cholesterol is processed.
    - One type of cholesterol is packaged in a nanoscale particle formed by a protein called low-density lipoprotein, or LDL. These particles can bump into a receptor on the surface of the cell, and the cell takes in the LDL.

    - If LDL isn't brought into our cells, then it remains in the bloodstream, and that's where it can cause harm. If the cholesterol is taken into the cell, then it can be metabolized.

    - Individuals who have a defect in one of the proteins that sends the cholesterol particles are susceptible to having high

serum cholesterol concentrations and subsequent coronary and vascular issues.

- Gold nanoparticles use the same pathway as LDL to enter cells. The particles bind receptor proteins on the outsides of cells and are taken in through pockets in the cell membrane. Interestingly, researchers have recently found that the shape and size of nanoparticles can affect the efficiency of uptake into the cell. This type of study is quite helpful as new nanomaterials are designed for applications that take place both inside and outside the cell.

Suggested Reading

Cooper, et al., *Principles of Protein Structure, Comparative Protein Modelling, and Visualization*.

de la Rica and Matsui, "Applications of Peptide and Protein-Based Materials in Bionanotechnology."

Stryer, *Biochemistry*.

Vo-Dinh, "Protein Nanotechnology."

Questions to Consider

1. What are the functions of proteins in cells? Why would it be important to interface them with nanomaterials?

2. How do we know what proteins look like at the nanoscale? Why does it matter?

Nanoparticles Detect Cancer in Living Organisms

Lecture 9

Some of the most exciting work in nanoscience first appeared, and is still taking place, in medicine. Now that we've taken a look at different types of biomolecules and how they can work together with nanomaterials, we're ready to look at a variety of applications where nanomaterials can be used in medicine. We'll start by looking at how nanotechnology is having an impact on the early detection of cancer, one of the most deadly diseases we contend with in the 21st century.

The Origins of Cancer

- There are 100 trillion cells in the human body, and the body makes 100 billion new cells every day. Every time a single cell divides, all 3 billion bases in the human genome need to be copied; that's 3 trillion bases that need to be copied per day.

- Recall from an earlier lecture that every strand of DNA is copied by a protein. The proteins that are assigned this function are fairly accurate, but they sometimes make mistakes, which result in mutations. In addition, if a person is exposed to radiation or a damaging chemical that can react with DNA, these mistakes or mutations may be even more frequent.

- Sometimes, such mistakes affect cells in ways that are harmless, but sometimes, a gene is modified in a way that affects how a cell divides and maintains itself, and once a mutation is made in DNA, it can be difficult to repair.
    - For example, free radical damage to DNA, which can be caused by radiation or chemicals, can cause the G residues in DNA to take on an extra oxygen atom.

    - When this happens, the protein that copies DNA mistakes this new form of G for a T, and when it synthesizes the strand across from it, the protein puts in an A instead of a G. This

G-to-A mutation is then perpetuated in all of the daughter cells, and it can affect the ability of the cell to self-regulate.

- If a DNA molecule that codes for a protein becomes mutated, then the new form of the protein that is produced may have some strange properties.
  - For example, the proteins called kinases attach phosphorus and oxygen to other proteins as a signal to tell the cell where it is in its life cycle.

  - If one of these kinases has a sequence that becomes mutated, it can become overactive. When that happens, the cell thinks it's time to divide earlier than it should, and it starts to divide at an accelerated rate.

- Mutated proteins can also cause cells to become dangerous by tricking them into ignoring signals that they're in trouble.
  - Normal cells know when they need to be turned over and replaced, but cells that have mutations in certain genes tend to ignore signals to turn over and become aggressive.

  - These cells divide too quickly, overtake the population in the tissue, ignore the signs that they're in trouble, and eventually, can form what's called a neoplasm, which is the start of a tumor.

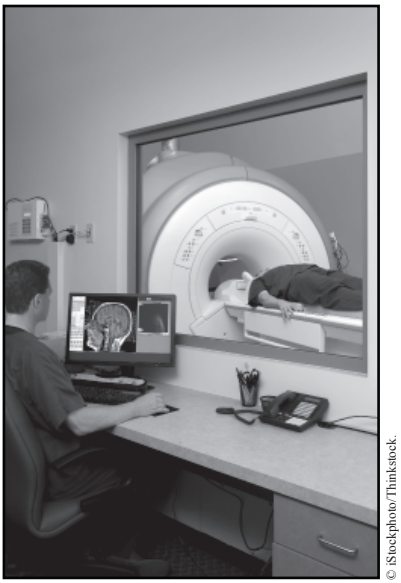
  - As we know, sometimes, tumors are harmless, but sometimes, the cells that form a tumor can become increasingly aggressive and invasive. Aggressive cells can even become detached from the primary tumor and ride through the circulatory system to another organ, such as the liver or brain.

Screening for Cancer

- Cancer is a disease that's treatable if it's caught early, but the methods we use to screen for cancer are not very good at catching the disease in the early stages.

- MRI is a good method for looking at a tumor after it has formed. Here, a patient is slid into a giant magnet, and all of the hydrogen atoms in the body are used to collect an image that can reveal a tumor. An amazing amount of detail can be collected with an MRI, but it is too expensive to use as a yearly screening method.

- How might nanotechnology be leveraged to find a solution? Biomodified nanomaterials may be used to find cancer cells, either while the cells are still in the body (*in vivo*) or as samples that have been taken out of the body.



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An MRI enables doctors to collect an amazing amount of detail; for example, every region of the brain can be imaged to find abnormalities or tumors.

Finding Tumors in Living Organisms

- The idea behind using nanomaterials to find tumors is to send tiny nanosensors into the bloodstream that are able to differentiate a cancer cell from a healthy cell. If the sensor finds a cancer cell, it could give off a signal that could be detected accurately.

- We've already seen examples of nanomaterials modified with specific biomolecules that make them able to recognize other molecules with very high levels of specificity. What types of molecules do we need to be able to recognize to know whether a cell is cancerous or not?
  - We can't target the mutated DNA because DNA is packaged up on the inside of the cell. A sensor that circulates inside the body can really only work with markers that are located on the

outside of the cell, such as the receptors we talked about in the last lecture.

- Certain types of receptors are often present at very high levels on the outside of cancer cells because these receptors are involved in signaling and in some of the self-regulation processes that go into overdrive in cancer cells. These receptors, then, are good markers that nanoparticles can be targeted to.

- One of the most sensitive ways to get a signal out of a sensor is to have it emit light, and as we've seen, quantum dots are effective materials for light emission. Another nice feature of these materials is that the color of their emission can be tuned across a broad range.
  - Because tissues also emit light, we need to think about whether the light emitted from the quantum dot will be visible so that it can be detected in the same environment as tissue. An absorbance spectrum of a typical tissue shows that light from the quantum dot can indeed make its way out to be detected.

  - In fact, nanomaterials are among the few materials that can absorb and emit light far in the red part of the spectrum, which is where it's necessary to be to get around the absorption and emission of natural tissue.

- To ensure that a quantum dot can find a receptor that is specific to a cancer cell, we rely on antibodies. These proteins can be engineered to stick to other proteins and can be covalently bound to the quantum dots.
  - As these quantum dots are swimming around in the bloodstream, they look for a cancer cell with many receptors on the surface. If they bump into a healthy cell, ideally, they won't see its receptor, which is at a much lower level on the surface of the cell, and they will just bounce off and go on their way.

- If they hit a cancer cell, there's a high probability that they will collide with a receptor and stick because the antibody has been engineered to stick to the receptor.

The Challenges of Quantum Dots

- This process works on both cells and tissue, but does it work in a living organism? Again, the ideal situation would be to inject into the bloodstream a solution of quantum dots that are specific for a certain type of cancer cell and let the dots circulate and find their target.

- If they didn't find a target, they would be excreted, and no signal would be emitted. If they came in contact with a tumor, they would stick and accumulate and could be detected by their light.

- One challenge here is that the human body is very good at filtration. Our kidneys filter our entire volume of blood every day 25 times! But the first demonstration of quantum dot–based visualization in a living organism was performed several years ago by researchers at Emory University.
  - These researchers generated three colors of quantum dots—green, yellow, and red—with each color specific for a different kind of tumor.

  - They then implanted tumors in lab rats and injected the three different solutions of quantum dots, all mixed together. Finally, they imaged the light coming out of the animals and were able to see the three types of tumors lit up.

- There were a few unexpected discoveries along the way to this advance that are quite interesting on their own. One is that there's a "magic" quantum dot size—4 nanometers in diameter—that allows this type of approach to conform to FDA regulations concerning the length of time in which materials must be cleared from the body.

- Another interesting discovery relates to the mechanism by which the quantum dots accumulated in the tumor.

- While we know that the matching of the antibody on the quantum dot surface to the cancer cell receptor helps targeting to be efficient and specific, it turns out that the structure of the blood vessels that feed oxygen to tumors also played a role.

- The blood vessels around a tumor are quite leaky because they experience pressure from the tumor. The small holes and breakages that result make it easier for a nanoparticle to get out of the blood vessel and into the tumor.

- The quantum dot approach has enormous promise for targeting tumors with nanoparticles and reading their signals from outside.
  - However, because quantum dots are very stable and because they are sometimes made with toxic materials, such as lead and cadmium, we need to look at the long-term effects of a quantum dot injection to ensure that we understand the risks.

  - These toxic materials are currently used because of their emissive properties, but researchers are now looking for alternatives, such as nanomaterials made from carbon.

  - Another challenge lies in the "scaling-up" of quantum dot–based materials for use in medical imaging. For this application, the synthesis of quantum dots must be highly reproducible and consistent.

Suggested Reading

Heath, Davis, and Hood, "Nanomedicine Targets Cancer."

Riehemann, et al., "Nanomedicine: Challenges and Perspective."

Weinberg, *The Biology of Cancer*.

Zrazhevskip, Sena, and Gao, "Designing Multifunctional Quantum Dots for Bioimaging, Detection, and Drug Delivery."

Questions to Consider

1. What signs do cancer cells exhibit that differentiate them from healthy cells? Why is it a challenge to read out these differences?

2. Why is the development of *in vivo* sensors (those that detect analytes within living organisms) so much more challenging than *in vitro* sensors (those that detect analytes in samples taken from a living organism)?

Detecting Only a Few Molecules of a Disease

Lecture 10

Testing for cancer inside the body using circulating nanosensors, as we discussed in the last lecture, is a promising approach that may eventually allow us to screen for cancer in a way that's completely noninvasive. But this approach is challenged by both regulatory hurdles and the fact that not all cancers respond equally well to *in vivo* testing. In this lecture, we'll look at *in vitro* testing, which offers a reduced regulatory burden and the ability to analyze cells or cancer markers in the blood.

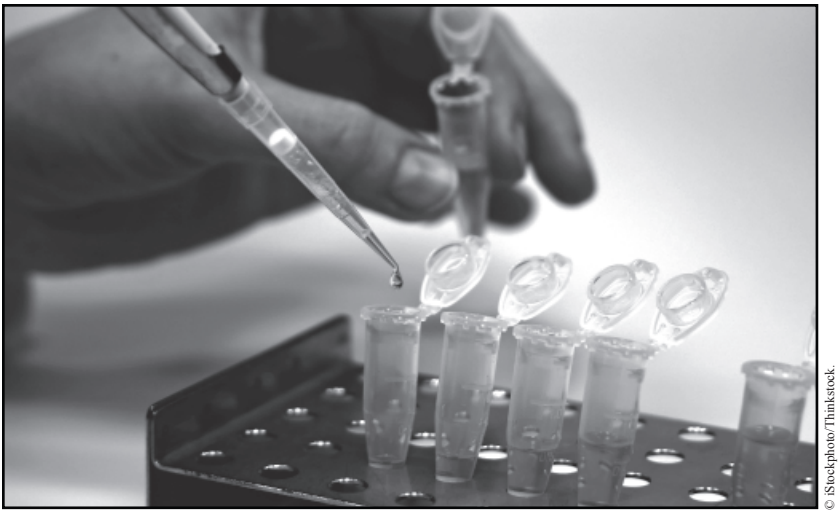
Early Cancer Detection

- Many of the tests currently used for cancer screening look for blood-borne markers and are performed *in vitro*, that is, outside the body. For example, the PSA test that is used for prostate cancer screening is performed using blood samples drawn from patients. This *in vitro* test and most others are not accurate or sensitive enough for early cancer diagnosis.

- The key feature that a testing strategy must have to be effective for early cancer detection is a very high level of sensitivity.
    - In a sample taken from a patient, the molecules that can be used as markers of cancer will be present at levels that are correlated with the burden of the disease or the size of the tumor.

    - If a tumor is small and still localized, it will not release many molecular markers into the bloodstream. With a blood cancer, such as one that affects the white blood cells, the cancer cells will be a tiny population compared to the red blood cells.

    - This means that if we're going to use a sample of blood for cancer screening, whatever method we use must be able to track very low levels of a targeted molecule in the presence of a background of excess cells and molecules that may interfere with the detection strategy.



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***In vitro* diagnostic tools using nanomaterials may appear sooner in clinical practice than *in vivo* approaches because of the reduced regulatory burden associated with this type of testing.**

- Nanomaterials show great promise for achieving this type of sensitivity. The fact that nanoparticles are almost the same size as proteins or nucleic acid molecules means that there is the potential for each particle to need only 1 molecule to make it give off a signal.

Nanosensors

- A research group at the University of Toronto has developed a powerful chip-based system that uses nanomaterials to very sensitively detect DNA sequences that are the markers of cancer.

- The chip is made using the same processes used in consumer electronics applications. The underlying substrate of the chip is silicon, and it has a gold pattern on it, generated using photolithography. On the surface of the chip are tiny holes that allow the introduction of nanomaterials.
  - The chips are placed in a bath of metal salt, and a potential is applied, which causes metal to electroplate onto the chip. As

the metal plates onto the chip, it forms nanostructures that are actually quite easy to manipulate.

- For example, using three different conditions for electroplating yields three different levels of nanostructuring.

- These chips can be used to detect biomolecules by, first, designing and synthesizing a DNA sequence that is complementary to the target for detection. That sequence is then attached to the sensor surface.
  - When the target sequence is present in a sample, it binds to the sensor through hydrogen bonding and base pairing. This binding event causes an electrical current to be given off, and that's what is measured.

  - A variety of sensors can be put on 1 chip to collect a profile of signals that can tell us about the type of cancer cell present in a sample.

- The presence of nanostructures on the sensors has a dramatic effect on the sensitivity of this approach.
  - With a smooth sensor, at least 1 million DNA molecules are needed in a sample in order for the sensor to give off a response. If the sensor has nanostructures measuring 20 nanometers, only 100 molecules in solution are needed to trigger detection.

  - The closer a nanostructure is in size to the molecules targeted for detection, the better the sensors work.

Testing the Chip-Based System

- Chronic myeloid leukemia (CML) affects the granulocytes (one kind of white blood cells) that are important for fighting infection. It's one of the most treatable cancers, but it's important that it is diagnosed and classified very specifically so that the right drug is used to treat it.

- This disease arises because a specific break occurs on chromosomes 9 and 22, and they then recombine to form a fusion. This creates a new DNA sequence that is not present in healthy cells. As a result of the presence of this sequence, a mutant protein is produced that causes the cells to be overactive and divide too quickly. This is what increases the number of white blood cells to a level that the body can't sustain.

- A drug is available that specifically targets this protein and shuts the mutant cells down. Because the mutant protein is present only in the leukemia cells, the drug has no effect on other cells and has few side effects.

- The method for diagnosing this type of cancer is expensive and slow and can be performed only in specialized laboratories by experienced laboratory technicians. For this reason, the microchip-based method was tested as a possible substitute. Instead of amplifying the CML gene, this method tries to turn up the volume of the signal that it produces.

- To test the chip-based approach for leukemia detection, a chip was designed that would display a DNA sequence specific to the CML gene fusion on a nanostructured sensor. The sequence was attached to the sensor by putting a sulfur atom at its end, enabling it to stick to the metal of the sensor. Once the chip was ready for a measurement, it was calibrated, and a sample was introduced containing an unknown number of cancer cells.

- The chip was designed to produce electrical signals that tell whether or not the target sequence is present. The chip also produces data that allow a determination of the levels of CML cells in the sample.

- The Toronto group has developed a prototype instrument to validate this sensing approach. Eventually, the chip will be embedded in a cartridge into which a physician can inject a sample. That cartridge will then be slid into the instrument, and the analysis will be

performed in about 5 to 10 minutes. The testing unit uses only a simple set of circuits to apply potentials to the leads on the chip and collect signals from the sensor.

Gold Nanoparticles in Cancer Diagnosis

- As we discussed, gold nanoparticles are good sensors to report on genetic disease and the presence of hormones that can confirm pregnancy. These materials can also detect proteins, making them powerful for cancer detection. The red color that a gold nanoparticle produces can be concentrated on a chip, and the fact that these red-absorbing nanoparticles are nanoscale makes them much easier to handle.

- A recent study using gold nanoparticles for protein detection looked at detecting PSA, the protein that is a marker for prostate cancer.
    - The commercially available PSA test is good at detecting large changes in levels of PSA, but it's not as good at looking for small variations or very low levels of the protein.

    - Men who are treated for prostate cancer with a prostatectomy have trace levels of PSA in their blood postoperatively that are not measurable using the existing test. But how fast the PSA comes back after the operation can tell a physician quite a bit about what treatment regime to use.

    - Again, the methods that are currently used for PSA screening simply can't look at these low levels. A study published in 2009 showed that the very sensitive gold nanoparticle approach could predict recurrence quickly and accurately.

- In this study, PSA detection data were collected for a large cohort of patients. The data sets showed a dramatic difference in PSA reappearance in different patients. For some, PSA levels stayed low after the operation, but for others, the levels started to creep up about a year after the prostatectomy.

- With prostate cancer, there are many treatment options that can be helpful for patients who aren't cured by surgery. And with access to the nanoparticle screening approach, oncologists have the information that further treatment is needed many months before they would know using conventional diagnostic assays.

***In Vivo* and *In Vitro* Approaches**

- *In vivo* approaches to cancer diagnosis may help us do whole-body screens for early tumors, while *in vitro* approaches provide information on cancer cells and markers in the blood.

- With the *in vivo* approach, we may be able to send nanosensors into a patient, let them circulate and accumulate in tumors, and then get a snapshot of the patient's profile. This approach has the promise of detecting tumors at very early stages.

- As we continue to develop *in vivo* methods, we will also use the *in vitro* approach. One of the unique advantages of working with a sample is that we can look for many markers at once, as opposed to just 1 marker with the *in vivo* approach.

Suggested Reading

Choi, Kwak, and Park, "Nanotechnology for Early Cancer Detection."

Giljohann and Mirkin, "Drivers of Biodiagnostic Development."

Questions to Consider

1. Contrast the conventional approach to *in vitro* cancer detection (making billions of copies of suspect DNA material) with the increased sensitivity to small amounts of potential cancer offered by nanotechnology. Explain for yourself how the newer approaches both resemble and differ from the fictional tricorder in *Star Trek*.

2. Based on what you know so far about current achievements in nano-based testing, speculate about what advances might be necessary to create a panel profile of *every* molecule in a cell.

Nanomaterials That Seek and Destroy Disease

Lecture 11

Science fiction fans may remember the movie *Fantastic Voyage*, in which a miniaturized submarine, complete with crew, zooms around a man's body to repair a blood clot in his brain. In this lecture, we'll see how gold nanoparticles are being used to achieve something similar—to target and eliminate diseased cells in living tissue. We already know that these particles can be modified to recognize specific molecules and diagnose disease; here, we'll see how they use heat-producing vibrations to kill cells.

Properties of Gold Nanoparticles

- Like quantum dots, gold nanoparticles are good at moving around the circulatory system, but how good they are depends on their size, which can range from about 1 nanometer to more than 100 nanometers. Studies have shown that smaller seems to be better in using nanoparticles to selectively eliminate diseased cells.

- What allows gold nanoparticles to kill diseased cells is their ability to absorb light and convert it into heat.
    - Recall that when quantum dots are photoexcited, the energy is released in the form of emitted light. It turns out that the electronic structure of quantum dots makes them good at holding the energy in an excited state that can be emitted as photons.

    - For gold nanoparticles, when light goes in, the energy comes back out as heat. This effect can be used to kill cells that gold nanoparticles selectively enter.

- Most biomolecules lose their shape when they're heated up, which interferes with their ability to function.
    - Several years ago, it was discovered that a 1.4-nanometer gold particle was exactly the right size to sit in the major groove of DNA, the larger of the 2 spaces between the 2 strands of DNA.

- If light causes a nanoparticle nestled in this space to give off heat, that heat will cause the 2 strands of DNA to dissociate, interfering with the cell's ability to function properly.

- Roughly the same thing can happen with protein molecules. Certain proteins will even nonspecifically attach themselves to gold nanoparticles, and these proteins can also be denatured when heat is produced. Thus, exciting gold nanoparticles with light can basically turn a good detection sensor into a sensor that can both seek and destroy a cell.

Gold Nanoparticles in Action

- Many types of cancer cells overexpress a protein called the epidermal growth factor. A team at the Georgia Institute of Technology attached an antibody to this protein to gold nanoparticles to study the particles' ability to achieve targeted ablation of cancer cells.

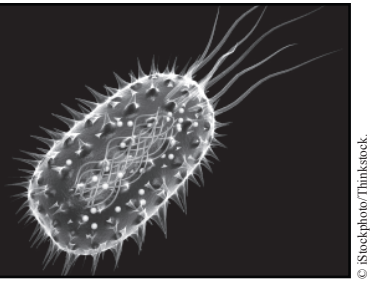
- The researchers first verified that the nanoparticles were very specific for cancer cells. To do this, they tested the activity of the nanoparticles with two types of epithelial cells, one healthy and one cancerous. Epithelial cells are those that line the surfaces of tissues, such as skin, and cavities, such as the mouth or the stomach. Healthy cells don't have much of the receptor that the particles were designed to bind to, while cancer cells have high levels of this receptor.

- The results of this research showed a distinct difference in gold nanoparticle binding to the two types of cells. When the researchers irradiated the particle-containing cells with light, they saw much higher levels of cell death for the cancer cells.

- This same approach can be used to selectively kill bacterial cells. In a study done at the University of Arkansas, researchers generated gold nanoparticles that carried an antibody specific to the bacterium *Staphylococcus aureus*.

- When these particles came into contact with the bacteria, they didn't penetrate the cell but sat on the cell membrane.

- When the particles were excited with a laser, they disrupted the cell and caused the bacterium to break open and die.



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Bacterial cells can be targeted for destruction by gold nanoparticles bound to specific antibodies.

The Challenge Presented by Living Tissue

- The challenge with using the gold nanoparticle approach to cancer or bacterial cell elimination in a living system relates to the issue of absorption of light by tissue that we discussed in a previous lecture.
  - Gold nanoparticles typically absorb light in the 500- to 600-nanometer range, and the larger the particle, the more that absorption shifts to a higher wavelength (the red part of the spectrum).

  - But in this part of the spectrum, there is a great deal of absorption by tissue. If the surrounding tissue is absorbing the light, that means that very little light will make it to the gold nanoparticles, even using a powerful light source, such as a laser.

  - Although gold nanoparticles give us an important proof of concept for using nanomaterials to target and damage specific cell types, this absorption of light by surrounding tissue appears to limit the use of gold in living systems.

- One way to solve the absorption problem is to make a modified type of gold-based nanoparticle, as was done by researchers at Rice University. Instead of using nanoparticles composed of gold, these researchers coated a core material, such as silica, with a thin layer of gold. This shifted the absorption of the particle far into the

infrared, which is a much better region of the spectrum for getting light to pass through tissue.

- As the coating gets thicker on these gold-based nanoparticles (nanoshells), the absorption peak shifts from the more red part of the spectrum to the more blue part of the spectrum, making these materials very tunable.

The Power of Nanoshells

- In a study done at the University of Texas Southwestern, a mouse model of prostate cancer was generated by implanting tumors that grow from human prostate cells. Once the tumors had grown to about 40 cubic millimeters, the mice were injected with gold nanoshells. After about 18 hours, the researchers irradiated the tumors with 800-nanometer light for about 3 minutes. They then measured the tumors over the course of 3 weeks.

- In the control group of mice that didn't receive treatment, the tumors tripled in size over this period. In the treated group, however, the tumors shrank so small that they couldn't be measured by the end of the 3-week period.

- Despite the success of this study, the researchers highlighted some limitations. For example, when they measured the penetration of infrared light into the tissue, they found that once they went further than 1 centimeter, they had trouble getting light into the tissue. Many types of tumors, such as lung or breast tumors, would need greater penetration depths than this in order to be accessible.

- One solution to this problem might be to deliver light directly to different places in the body, for example, by bringing a fiber optic bundle into the lung. But instead of using visible or infrared light, we might also think about using a different type of radiation that doesn't have these absorption problems.

Gold Nanoparticles as Antennae

- One of the most common methods of cancer treatment relies on radiation therapy. Here, much smaller wavelengths of light are used to directly damage cancer cells.
  - This therapy is called ionizing radiation because when it hits molecules, they are forced to give up electrons, becoming charged ionic molecules. This, in turn, triggers DNA to release electrons and causes it to self-destruct.
  - This type of external beam radiation therapy is very effective at shrinking tumors and is much easier to get through human tissue. But it's often difficult to cleanly target the tumor because there are always healthy cells in the vicinity.
- The fact that we can make gold nanoparticles specific for cancer cells gives them the potential to be used as antennae for ionizing radiation, to help radiation therapy be more selective for tumor cells versus healthy cells.
- The dose enhancement effect comes into play when radiation interacts with the junction between two materials that have different atomic numbers.
  - At the interface between gold (atomic number 79) and the atoms of human cells (atomic numbers ranging from 1–8), very high doses of radiation will be generated.
  - We've seen that gold nanoparticles can be directed at cancer cells, bind them, and enter them selectively, and here, we could potentially use the good penetration properties of ionizing radiation to more effectively get at tumors that are buried under skin and tissue but leave healthy cells untouched.
- Scientists at the University of Connecticut Health Center, collaborating with a company called Nanoprobes, were among the first to explore how ionizing radiation could be used in combination with gold nanoparticles. In a study of mice implanted with breast cancer tumors, treatment with a combination of gold nanoparticles

and radiation eliminated the tumors and resulted in a survival rate of 86% 1 year after treatment.

Gold Nanoparticles as an Internal Source of Radiation

- Using gold nanoparticles as an internal source of radiation eliminates the need to have radiation passing through healthy tissue at all; thus it's even cleaner than the amplifier approach of using the particles in combination with radiation.

- The use of radioactive particles to shrink tumors is referred to as brachytherapy. This approach is particularly effective for the treatment of prostate cancer. It is much less invasive than surgery and much less prone to complications. It can also be used to make surgery more straightforward by shrinking the tumor before a surgeon tries to excise it.
    - Here, small seeds made of radioactive gold are implanted near a tumor. The overall effect that results, the death of cells close to the particles, is the same as what's achieved with external radiation, but it's much more localized and doesn't affect healthy cells.

    - One problem with this approach is that the radioactive seeds can be difficult to work with and exhibit a great deal of variability in size. Seeds of varying sizes are less likely to focus on the tumor and more likely to focus elsewhere, perhaps causing inflammation, pain, and other side effects.

    - Of course, as we know, it's pretty straightforward to precisely control the size of nanoparticles. Thus, well-defined nanoparticles made of radioactive gold could greatly improve the reproducibility and reliability of brachytherapy.

- A group at the University of Missouri tested the efficacy of radioactive gold nanoparticles for brachytherapy. They were first able to show that the gold nanoparticles had very little variation in their sizes, especially compared with conventional gold seeds, and in the levels of radioactivity they emitted. Further, the volume

of prostate cancer tumors in mice treated with the radioactive gold particles was reduced by about 82%, with no side effects.

- This discovery may present a way to effectively deal with tumor metastases, particularly micrometastases, which are difficult to detect using imaging. Radioactive gold nanoparticles could actually find tumors and shrink them, irrespective of size—a much more effective way to halt the progression of metastatic cancer.

Suggested Reading

Kennedy, et al., "A New Era for Cancer Treatment."

Kumar, ed., *Nanomaterials for Cancer Therapy*.

Morton, Day, Halas, and West, "Nanoshells for Photothermal Cancer Therapy."

National Cancer Institute, "NCI Alliance for Nanotechnology in Cancer."

Questions to Consider

1. What are the advantages and disadvantages of using nanomaterials, such as gold nanoparticles, in medical testing?

2. Which of the three broad approaches to using nanomaterials against cancer do *you* regard as most promising? Why?

How Nanomaterials Improve Drug Delivery

Lecture 12

Have you ever thought about what happens to a pill once it lands in your stomach? Think, for example, about aspirin—in addition to curing your headache, it may also give you a stomachache. The way we administer drugs is often untargeted, which can lead to side effects. In this lecture, we'll look at how nanomaterials may be used to allow more targeted drug delivery.

The Challenges of Drug Delivery

- Getting a drug to work in the human body is all about getting it to the right site at the right level. The reason this is difficult is that we almost always rely on a delocalized means of distribution.
    - In all of our drug delivery methods, the drug has to pass through a barrier, which may be the small intestine, the tissue in our ears or eyes, or the epidermis of our skin. Our bodies have several kinds of densely packed protective cells, and the drug must be able to get through these barriers and into the bloodstream.

    - In addition, many drugs don't survive the acidic conditions of the stomach. In these cases, drugs are typically injected into the bloodstream, but this is not a particularly well-liked means of administering drugs.

- Drugs that are injected into a vein go first into the heart and then to the lungs, along with the blood, to get oxygenated. Once it picks up oxygen, the drug will then travel through the body in the arteries and flow into the capillaries. This is where the drug has the opportunity to make it into a tissue. Capillaries are about 10,000 nanometers in diameter, so nanoscale drug particles can easily flow through them.

- Among the toughest challenges in drug delivery are those encountered in anticancer therapy. Tumors are difficult to penetrate, in part because the blood supply reaches only the outside of the tumor. In addition, many of the drugs used to treat cancer have significant toxicity if they reach healthy cells; thus, it's important to engineer some type of targeting into their delivery.

- In the scenario in which a drug is circulated by tagging along with blood, it will go through the lungs, liver, heart, and kidneys as it travels, and there are many harmful things that can happen to these organs when they're exposed to drugs. If we are trying to target a drug to the pancreas, for example, it would be best to send it right there and not have it pass through any other organs.

- It's also true that many drugs are difficult to formulate; for example, some drugs are difficult to make into powders, so they can't be made into pills. For intravenous drugs, sometimes the solvents that are needed to get a greasy drug molecule into solution can have more side effects than the drug itself.

Drugs in Current Clinical Use

- Only a few classes of drugs are used for cancer chemotherapy.
    - Some of these are molecules that react with DNA; this is a good approach for an anticancer drug because it can shut down rapidly dividing cells by depriving the cells of instructions for making more copies.

    - Other drugs interact with structural components of cells, interfering with cell division.

    - Yet another approach to cancer chemotherapy involves molecules that act like natural metabolites and interfere with DNA synthesis. They shut down the enzymes that are responsible for copying DNA and, again, deprive the cell of instructions needed to replicate further.

- Cisplatin is a drug used to treat ovarian cancer, lung cancer, leukemia, and quite a few other cancers. The activity of cisplatin is termed DNA alkylation, which basically means that the drug hits one of the functionalities on the DNA base and interferes with its structure. Because they affect both normal and cancerous cells, DNA alkylators would definitely benefit from more specific delivery.
    - Cisplatin was first characterized in 1845, and in the 1960s, it was found to stop cells from replicating. It was approved as an anticancer agent by the FDA in 1978.

    - Cisplatin has a range of side effects, including kidney problems, hearing loss, weight loss, and nausea; thus, minimizing the exposure of healthy cells to cisplatin would be beneficial.

- Another effective anticancer drug is doxorubicin, used to treat certain leukemias, bladder cancer, breast cancer, tissue sarcomas, and others. Doxorubicin works by slipping in between the DNA base pairs and shutting down the DNA copying, which helps to shut down cell division.
    - Doxorubicin was originally isolated from a microbe that has a bright red color. The bug that produces it probably uses the molecule to fight off other bugs. It was originally thought of as an antibiotic, but later it was discovered to have antineoplastic activity, or anticancer activity.

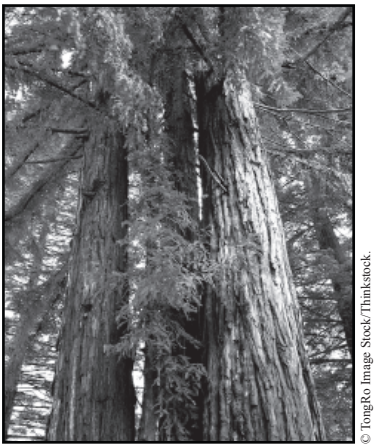
    - The main problem with using doxorubicin is that it causes damage to the heart and lungs. The cardiotoxicity that's seen after doxorubicin treatment is a major side effect and can actually be life-threatening once a certain dosage is reached. It's important, then, to find ways to keep doxorubicin out of the heart.

- TAXOL®, originally derived from the bark of the Pacific yew tree, is widely used for the treatment of lung, ovarian, and breast cancers. TAXOL works by binding to a cell's microtubules, parts of the cell that are important for structure. When TAXOL is bound, the

cytoskeleton of the cell can't be broken down to make way for new cells. This is another way to shut down rapidly dividing cells.

- The major problem with using TAXOL is that it is a large, greasy molecule. It's very hydrophobic, which makes it difficult to formulate.

- Castor oil is used to make TAXOL stable in solution, but when castor oil is injected intravenously, it can cause some people to experience neurotoxicity.



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A program in the 1950s to find naturally occurring drugs resulted in the development of paclitaxel, a drug derived from the Pacific yew tree and used to treat lung, ovarian, and breast cancers.

Nanoscale Drug Carriers

- A carbon nanotube looks similar to a drug capsule, and nanotubes are hydrophobic, which means that drug molecules that are difficult to formulate will work well inside carbon nanotubes. As we've mentioned, carbon nanotubes can be biodegraded. It's also possible to cork carbon nanotubes—to snip the ends shut but have them open back up once they're in the right environment. Further, nanotubes can also be coated with drugs on the outside.

- Liposomes represent another major class of nanoscale drug carriers. Liposomes are soft materials, mainly made out of the lipids that make up the membranes around all of our cells. Drugs are encapsulated inside the lipid bilayer. Again, these carriers offer excellent biodegradability.

- Protein nanoparticles are also great vehicles for delivering drugs because not only are they biodegradable, but the cells recognize them as just being proteins. If we can find a way to make a particle

out of protein and fill it with a drug, it would be an effective way to move a drug around the body and get it to tumors very specifically.

- Nanomaterials are also good at getting around some of the resistance mechanisms in cells, which can be a major problem. Cancer cells are very aggressive and can pump drugs out of cells; they can also introduce enzymes that will deactivate drugs. But packaging drugs in nanomaterials disguises the drugs from the cancer cells.

- Nanovalves sense pH levels, which differ in healthy cells and cancer cells. If the nanovalve senses the pH of a cancer cell, only then will it release the drug into the cell.

Studying Drug Delivery with Nanomaterials

- The most popular way to study drug delivery with nanomaterials is to use cultured cells. Such studies look at the effects of drugs with and without the nanomaterial-based carrier.

- Once we have some proof of principle with cultured cells, we can then move into an animal to see if we can reproduce the same effect, but here, we have the circulatory system to contend with and all the other intricacies of a live animal.

- Another way to study drug delivery that's unique to using nanomaterials as delivery agents is to use scanning electron microscopy. Here, we use a particle that can be seen as a carrier and then image the cells we're testing to determine exactly where the particle went. This gives us a full profile for what's happening at a very fine level.

Suggested Reading

Allen and Cullis, "Drug Delivery Systems."

Ferrari, "Frontiers in Cancer Nanomedicine."

Hillery, Lloyd, and Swarbrick, eds., *Drug Delivery and Targeting*.

Langer and Folkman, "Polymers for the Sustained Release of Proteins and Other Macromolecules."

Questions to Consider

1. Why can't every drug be packaged into a pill?

2. How can nanomaterials help with drug delivery? What's special about their properties that provides a solution in this area?

Delivering Drugs with "Smart" Nanocapsules

Lecture 13

In the last lecture, we looked at some of the powerful drugs that are available to fight cancer and discussed the challenges of delivering drugs within the human body. We also examined a variety of carriers, including nanotubes, liposomes, and others, that are potentially programmable to bring drugs to specific tissues. In this lecture, we'll look at some recent studies in which these nanomaterials have been shown to be effective in improving drug activity.

The FDA Approval Process

- Many of the studies we'll look at in this lecture are preclinical trials. These studies are typically done in academic labs to test whether modifications to an existing drug or a completely new drug show significant activity.

- Once the preclinical data are collected on cultured cells and mice, the next step in the FDA approval process is to organize a Phase 0 clinical trial. This study is conducted on a small number of patients and is designed to enable researchers to quickly understand what a drug does to the body and what the body does to the drug.

- Next, a Phase 1 trial is conducted. This trial uses a large group of healthy volunteers to assess the safety of a drug. The thinking here is that if a healthy person can't tolerate a drug, it's unlikely that someone who is sick will, particularly a cancer patient.

- If everything goes well with the healthy volunteers, the Phase 2 trial then looks at how well the drug works in a cohort of cancer patients. Here, information on how the drug should be dosed is also collected.

- If effectiveness is observed in Phase 2, then a large a Phase 3 trial is set up. Here, testing is conducted with a large group of patients;

half of the group is given the drug and the other half is given a placebo. Because the improvements in survival can be small in drug trials, especially cancer drug trials, it's important to look at placebo effects.

- If the results of a Phase 3 trial are positive, then the drug will typically be approved by the FDA. This entire process can take about 8 years, and the preclinical work with mice needed before a trial can be started can take about 6 years. For every 1000 drugs that begin preclinical testing, only 1 goes to clinical testing.

DOXIL®

- The drug DOXIL, coupled with a nanoscale carrier, has made it through the FDA approval process and into clinical use. DOXIL is based on doxorubicin, which as mentioned earlier, causes cardiotoxicity and can impair heart function.

- In the 1990s, researchers at the University of San Francisco and a small company called Sequus Pharmaceuticals developed a new form of doxorubicin packaged inside a liposome. The drug molecules inside this nanoscale package are held in place by a lipid bilayer and a layer of polyethylene glycol.
    - The lipid bilayer keeps water on the inside of the particle. The polyethylene glycol helps the particle stay in circulation by keeping the immune system from attacking it.

    - This liposomal packaging system helps a dose of the drug stay in the body longer. This means that the drug has more time to find the tumor and that repeated doses aren't necessary, which seems to have lowered cardiotoxicity.

- Cardiotoxicity also seems to be suppressed as a result of the nanoscale structure of DOXIL. Because they are larger than regular molecules, the DOXIL particles are kept out of the crevices of the heart where they can do damage.

- DOXIL also takes advantage of the passive tumor-targeting effects that we've discussed. It was approved by the FDA in 1995 and has been shown to be particularly effective in treating Kaposi sarcoma, a skin tumor often seen in AIDS patients.

TAXOL

- As we discussed in the last lecture, the drug TAXOL is made into a liquid formula by dissolving it in a form of castor oil, Cremophor®. The drug itself, which binds to microtubules and disrupts the replication of cancer cells, has a fairly good side effect profile, but Cremophor may cause neurotoxicity. To make matters worse, Cremophor can also dissolve the plasticizers in the tubing that is used to administer the drug intravenously.

- A company called Abraxis has developed a form of paclitaxel that allows it to be administered without any toxic solvents; this form is packaged into nanoparticles of the protein albumin.
    - This protein is water soluble, occurs naturally in humans, and has a tendency to form nanoparticles that are about 100 nanometers in size.

    - Even more important, albumin can bind to receptors in blood vessels and give them a signal that allows the drug-protein complex to travel out of the blood vessel.

- The activity of the drug is very impressive. In a trial focused on metastatic breast cancer patients, the tumor response rate was twice as good for the nano-formulated drug. Dramatically reduced side effects have also been shown. This form of paclitaxel was approved by the FDA in 2005.

Dual-Layer Nanoparticles

- A study done at MIT and reported in 2005 showcases the advantages of nanomaterials. This study involved nanoparticles with 2 layers—a core of doxorubicin and an outer layer with a molecule that interferes with angiogenesis, a process by which new blood vessels are made.

- The efficacy of these dual-layer nanoparticles was tested in a mouse model of melanoma. When the mice were treated with either doxorubicin or the anti-angiogenesis agent on its own, they survived for only 20 or 30 days. With the combined nanoparticle, they lived three times as long.

- Without the control to make these nanoscale layers, this type of approach wouldn't be possible. This is why nanotechnology is so powerful: because it allows us to manipulate things at a fine level that can make a significant difference for drug delivery.

Next-Generation Nanodelivery Systems

- Researchers at Duke University are currently developing a peptide-based nanoparticle that has produced dramatic results as an anticancer treatment. They started off by engineering a peptide that would self-assemble around the drug doxorubicin.
    - A domain on these peptides has a section that has a good ability to grab the drugs. On the other side of the peptide is a group of hydrophilic amino acids.
    - In a solution of these peptides and a drug with water, the drug and the sticky part of the peptide go inside, and the hydrophilic part of the peptide goes on the outside. The result is a water-soluble particle with the drug encapsulated inside it.
    - These peptides will spontaneously form 100-nanometer particles, a good size for a drug delivery system.
    - A single dose of these nanoparticles increased the 60-day survival of mice with tumors by 90%.
    - These researchers also discovered that the conjugates are good at preventing cells from becoming drug-resistant, likely because the drug is very fast-acting.

- A group at Northwestern University has come up with the idea of producing nanobins that can sense pH and selectively release a drug in response to a pH change. To create these bins, the researchers developed

a polymer that could be cross-linked to hold the particle together, which allows them to load the particle with doxorubicin.

- Because they are pH-responsive, the bins shrink when the pH is lowered. In other words, as pH goes down, the bin collapses on itself and eventually squeezes all of the drug out. As we've said, cancer cells have a lower pH than healthy cells.

- These nanostructures worked extremely well in tests in a mouse model of breast cancer.

- A group in Japan has done some interesting work with carbon nanohorns to deliver cisplatin. These nanohorns bind to the surface of the cell and seem to be able to poke through the cell membrane and deliver the drug directly into the cell. The researchers in Japan showed that the potency of the drug improved by about sixfold in a mouse model, and there was no weight loss in the mice, which is a common problem with cisplatin.

- At Stanford, a group is working with using carbon nanotube transporters. As mentioned earlier, a small amount of drug can be contained inside a nanotube or adhered to the outside and released when it reaches its target. In a test of the latter approach in a mouse model of lymphoma, tumor growth was completely arrested and there was decreased damage caused by the drug in non-tumor sites.

- Finally, a group at MIT has developed a targeted polymer nanoparticle. In addition to an anticancer drug, this system incorporates a recognition domain that allows the particle to specifically pick out prostate cancer cells, which have a special protein on the surface. In a test with mice, prostate tumors virtually disappeared.

The Future of Nanoscale Drug Delivery

- Of all the examples we've see in this lecture, the one with the most specificity—the one that had a recognition element that was able to specifically bind to prostate cancer cells—was the one that achieved the most dramatic results. It's likely that obtaining heightened specificity to lessen effects on healthy cells will be an increasing focus of this field.

- It's also important to note that nanoscale drug delivery has applicability in a variety of disease states—not just cancer—and there is interesting work going on in a number of different areas, such as cardiovascular medicine and treatment of diabetes.

- In general, it's clear that the pace of progress in nanoscale drug delivery is rapid, and it will likely continue to produce exciting advances in the short term.

Suggested Reading

Peer, et al., "Nanocarriers as an Emerging Platform for Cancer Therapy."

Petros and DeSimone, "Strategies in the Design of Nanoparticles for Therapeutic Applications."

Weintraub, "A Nano Drug's Giant Promise."

Questions to Consider

1. What's the difference between using a macroscale capsule for a drug and using a nanocapsule? Why would the activity of the same drug in these two forms differ?

2. How do nano-based drug delivery approaches limit side effects?

Nanoscale Surgical Tools

Lecture 14

Surgery is currently the most effective and widely used procedure in treating human cancers and other diseases, but to be curative, surgery must be incredibly precise. Incomplete removal of a tumor can decrease survival rates significantly. In this lecture, we'll look at nanoscale surgical tools, such as tweezers and scalpels, that will improve the precision of surgery, as well as nanomaterials that enable more accurate diagnosis and aid in healing.

Assessment of Tumor Margins

- In order to completely excise cancer, a surgeon must be able to identify tumor tissue and distinguish it from healthy tissue. Where these two types of cells come together are called the "margins" of a tumor. It's important to take as little of the healthy tissue as possible, because there could be important nerves or blood vessels in the tissue; thus, surgeons are very conservative in taking extra tissue.

- Typically, when an operation is complete, a surgeon will take a small sample of tissue that he or she considers to be outside the margins of the tumor for post-surgery testing. In breast cancer, up to 50% of partial mastectomy cases require a second procedure because tumor is found in such samples, and in early-stage lung cancer, residual tumor deposits after surgery are associated with up to a 35% reduction in survival.

- The limiting factor in detecting microscopic tumors or defining the borders of a tumor at the time of surgery is the sensitivity of the human eye, which can resolve only objects that are about 250 microns in size. Further, tumor cells are not usually visually distinct from healthy cells, making them even more challenging to selectively remove.

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Nanotechnology has significant potential to improve what happens before, during, and after surgery; nanoscale tools and materials can aid diagnosis, enhance surgical precision, and speed recovery.

- In 2002, a group of researchers at Massachusetts General Hospital and Harvard Medical School showed that iron nanoparticles could be used to improve surgical removal of brain tumors in lab animals.
  - Here, iron oxide nanoparticles helped with visualization of brain tumors before surgery using MRI and included a chemical dye that would emit light on excitation to light up the tumors during surgery.
  - Once the surgery was done, the researchers performed postmortem testing and determined that all of the cancer cells were gone.
  - In order for these nanoparticles to work, they had to cross the blood-brain barrier, a shield of capillaries around the brain. Molecules measuring about 1 nanometer, such as sugar,

alcohol, and nicotine, can penetrate this barrier, but typically, larger molecules cannot. Surprisingly, the iron nanoparticles—measuring 50 nanometers—were able to pass through.

Visualization of Lymph Nodes

- The lymphatic system is a network of vessels that carries lymph, a fluid that contains much of the waste generated by cells and is used to transport foreign cells to the lymph nodes, where they can be destroyed. The lymphatic system provides another route for cancer cells to move around the body.

- With some cancers, before they spread to other parts of the body, their first stop is a lymph node or gland close to the tumor. The lymph node closest to the tumor is referred to as the sentinel lymph node (SLN). The idea behind surgery on SLNs is to see if the cancer has spread.

- The way that SLNs are typically imaged for surgery involves the injection of a radioactive tracer near the tumor. A Geiger counter can then be used by the surgeon to track the tracer as it moves into the SLN. Using radioactivity for this procedure is not ideal because, of course, radioactive substances can be harmful. But nanomaterials may be able to provide an alternative solution.

- In 2006, researchers noticed that when infrared-emitting semiconductor quantum dots were injected into a tumor, they localized directly to the SLN. The quantum dots clearly found the same path that metastatic cancer cells take through the lymphatic system to reach the SLN. The time required for the lymph nodes to light up was only 15 seconds, which would allow a surgeon to visualize the right lymph node and take samples for biopsy in real time.
    - The pig model system used for these trials is the Sinclair™ Miniature Swine, a type of pig that has been engineered to spontaneously develop melanoma. Melanoma is a relevant type of cancer for SLN mapping because about 70% of melanomas in humans metastasize by passing through the lymph nodes.

- The pig form of melanoma is similar to the human form, making this system relevant for testing the quantum dot imaging approach.

- Another feature of these pigs that is indirectly useful is that they have highly pigmented skin and dark hair, which makes detecting light given off by the quantum dots difficult; thus, getting proof of principle in this system makes it that much more likely that it would work in humans.

- The use of nanomaterials to find lymph nodes is likely several years away from application in humans, but the potential for impact on surgical outcomes is significant. Lymph node resection is one of the most difficult things for surgeons to learn when they use existing techniques for visualization. Being able to use nanoparticles to illuminate lymph nodes should make the learning curve much less steep.

Robotic Surgery

- The most common types of robotic surgeries actually have a human being controlling the robotics, but using the robot as an interface to the patient helps eliminate tremors and allows for finer manipulations. One thing robots lack, however, is a sense of touch, and for most types of surgery, this is quite important.

- A device that may be able to give robots a sense of touch is a kind of nanoparticle sandwich, with 2 layers of gold nanoparticles on the outside, a layer of cadmium sulfide on the inside, and a layer of squishy plastic separating the 2 kinds of particles.
  - When stress is placed on the gold nanoparticles on the outside, they couple with the cadmium sulfide, causing light to be emitted. In a sense, the particles can feel the presence of others.

  - Someday, this type of device may allow a robot to be able to "feel" the tissue that it's operating on and sense fine features within the tissue.

Nanoscale Surgical Tools and Medical Nanomaterials

- A 1999 study reported in the journal *Science* described a clever approach for manipulating nanomaterials at the macroscale for medical uses.
    - In this study, a 1000-nanometer glass rod was attached to 2 carbon nanotubes, with the attachment sites made of metal so that they could serve as electrodes.

    - When there was no potential applied to the electrodes, the carbon nanotubes remained apart. But when 8 volts were applied, the tips of the 2 nanotubes were drawn together.

    - This device acts just like a pair of tweezers and could be able to pick up a single cell.

- Another way that increased precision could be achieved during surgery is through the use of nanolasers. Very fast and focused laser pulses are able to target single cells or even substructures within cells. This type of approach has been used to cut single nerves in worms that are just 1 millimeter in length.

- Brain researchers have also discovered a new nanomaterial that could be effective at stopping bleeding during neurosurgical procedures and other types of surgery. This material is a peptide that self-assembles into a nanofiber. It may someday be an important tool for treating acute trauma or could even replace the Band-Aid®.

- Nanomaterials can also be used to speed wound healing and limit infection. Silver nanoparticles, which kill bacteria, are particularly promising for this application.
    - In a study comparing silver nanoparticles with antibiotics for treating burns, the burns healed 4 days earlier when treated with silver nanoparticles, and scarring was reduced.

    - Having silver present as a nanoparticle seems to enhance the effect of the metal. The nanoparticles may fool the immune

system into not overdoing the immune response, which cuts down on inflammation.

- In addition to promoting healing, nanoparticles can also be used to solder a cut shut, eliminating the need for stitches. In a study at Rice University, researchers applied gold nanoparticles to cuts in rats, then exposed the nanoparticles to 800-nanometer near-infrared light and heat-soldered the wounds shut. There may be the potential to use a similar approach to repair nerves or blood vessels.

- Clearly, there is significant potential for nanotechnology to improve what happens before, during, and after surgery. Many types of tools are becoming available to make surgery more precise, and recovery from surgery may be sped up using better agents for wound healing and treatment. Although we've focused on cancers, similar kinds of techniques have begun to make progress for cardiovascular diseases, as well.

Suggested Reading

Asiyanbola and Soboyejo, "For the Surgeon: An Introduction to Nanotechnology."

Ben-Yakar and Bourgeois, "Ultrafast Laser Nanosurgery in Microfluidics for Genome-Wide Screenings."

Jain, *The Handbook of Nanomedicine*.

Singhal, Nie, and Wang, "Nanotechnology Applications in Surgical Oncology."

Questions to Consider

1. What are the greatest challenges surgeons face? Which presents more problems postoperatively, the surgical procedure or the healing process? How can nanomaterials and nanotechnology help in both of these areas?

2. How can nanomaterials aid the precision of the human eye and human hand?

Nanomaterials for Artificial Tissue

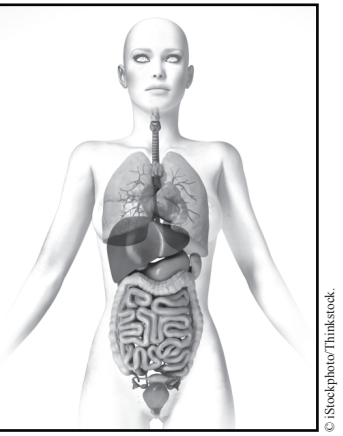
Lecture 15

The field of regenerative medicine, or tissue engineering, focuses on producing artificial substitutes that could restore or replace damaged tissues or organs. We've known how to transplant organs for decades, but transplants are extremely difficult, and a limited supply prevents all who need new organs from receiving them. In this lecture, we'll review a collection of promising discoveries demonstrating that the future of medicine for damaged tissues and organs could be very different from the present.

Natural Tissues and Organs

- Simple kinds of tissues, such as skin and cartilage, are readily made using methods analogous to those for culturing cells in the laboratory for research. Although we can grow cells and layers of cells, we're still not good at putting cells together into more complicated structures.

- The building blocks of tissues and organs must be organized. In other words, the cells must be oriented in specific directions, and certain types of cells need to be interfaced in a particular way. Further, tissues and organs need blood vessels and nerves. It's difficult to build up a structure made of 1 kind of cell, but it's even more difficult to build up structures in which the components are made of many different kinds of cells.



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Demand for organ transplants can exceed the supply from donors by more than 300%, but nanoscience is being used to advance the field of tissue engineering so that we may one day be able to generate artificial organs.

- To self-organize in the body, organs and tissues take advantage of cues in their environment to "know" which direction to spread out in. To generate artificial tissues, it's necessary to provide scaffolds that will bring cells together and allow them to interact in such a way that functional tissue will grow.

- In human beings, the scaffold is a complex network of proteins that provides an environment conducive to cell growth. This scaffold is called the extracellular matrix. Collagen is a major component of the matrix.
    - The extracellular matrix looks somewhat disorganized, but it's actually a highly organized structure. Each protein is in a precise location so that it can guide a cell to grow in a certain direction.

    - This matrix also binds factors that may stimulate and provide instructions for directional growth.

    - In recent years, scientists have been able to separate all the cells of an organ from its extracellular matrix. Incredibly, cells can be regrown using the matrix as a scaffold, and the functionality of the organ will return. In 2010, a lung regenerated in this way was transplanted in a rat.

- It seems that if we could re-create the extracellular matrix from synthetic components, we would be able to generate new organs. The formation of this matrix, however, is a precise, programmed biological process, and unfortunately, we do not yet know how to re-create it.

Nanostructuring

- One approach to engineering nanomaterials to create the extracellular matrix is to use different nanopatterns on surfaces to grow cells oriented in specific ways. Just a few years ago, a team at MIT showed that nanopatterning on a hard surface could have a dramatic effect on cell orientation.
    - This group compared cell growth on nanostructured and non-nanostructured substrates and found that cells on the

nanostructured substrates seemed to "know" that they should stretch in the same direction as the nanoscale pattern.

- In nature, the fibers in collagen line up in a pattern that looks very much like the nanograting used by the team at MIT.

- The same group at MIT also studied how the growth of endothelial progenitor cells (EPCs) was affected by the presence of a nanopattern. EPCs are the precursor cells that form the inside of a blood vessel. When grown on a flat surface, these cells were unable to organize into useful vessels, but on the nanograting, long vessels were formed.

- Researchers at Seoul National University in Korea have shown that nanoposts work well for this application, too. In this study, cells called fibroblasts threaded themselves through a nanograting with posts that had a particular spacing. Fibroblasts are cells in the body that produce collagen, a material important to the extracellular matrix.

Self-Assembling Nanomaterials

- One example of a self-assembling nanomaterial that could be relevant to regenerative medicine is a peptide nanofiber that forms a gel made up of long fibers. The nanoscopic structure of this gel closely resembles the extracellular matrix.

- Among the first cell types tested for growth on this artificial version of the extracellular matrix were neural progenitor cells (NPCs), which mature into neural cells. If it was possible to get NPCs to grow into a precise structure, they could be used to repair central nervous system damage.
  - Nerve cells are not good at regrowing; thus, the gaps that are formed during injury, for example, in the spinal cord, persist, causing breaks in the communication that is essential for the function of the nervous system.

  - Nervous system tissue is a complicated network of fibers and neurons that send electrochemical signals over long distances. As a result, neurons have a much more complex structure than

most other cell types and are difficult to grow in the lab or into the fibers found in the human body.

- To test whether a peptide nanofiber could assist with generating artificial nerves, a group at Northwestern University mixed the peptide with a solution of NPCs and allowed the peptide nanofibers to self-assemble around the neural cells. This environment enabled the researchers to grow NPCs much more efficiently.

- With this promising result, the same group then tested whether this material could repair spinal cord injury in mice. Mice who received a treatment of peptide nanofiber after spinal cord injury recovered about 90% of their normal functions, and scarring—which is a significant problem in spinal cord injury—was minimized.

- Another study done as a collaboration between a group at MIT and a group in Hong Kong used an analogous peptide-based material to look at the possibilities for restoration of vision.
    - This study involved cutting a specific nerve axon in mice that's essential for vision, then treating them with the peptide nanofiber and measuring their responses to visual stimuli.

    - In a control group, the mice got back only about 10% of their vision, but the group treated with the nanofiber got back 80%.

Synthetic Organs

- The liver is an essential organ that detoxifies blood, produces proteins and hormones, and provides molecules needed for digestion. About 80% of the cells in the liver are hepatocytes, which synthesize essential proteins and hormones and break down chemicals, such as drugs.

- In order for hepatocytes to do their work on all of the blood in our bodies, the cells must be in close contact with the blood running through the circulatory system; thus, the liver has as an intricate system of vessels running through it.

- The vessels are organized into repeating hexagonal columns that have a central vein running through the center of each column. Then, the arteries are located at the junctions between the columns. There are also ducts that run through the liver that transport bile, one of the most important molecules made in the liver.

- One of the first attempts to make an artificial liver involved a device that had a collection of tiny channels that could pump blood. The channels were made of a porous material, with liver cells grown on top. The liver cells weren't given any external sources of food, but they were clearly able to extract nutrients from the blood. The hepatocytes also excreted proteins into the blood; in other words, the basic level of functionality was present.
    - The researchers then increased the throughput of this device by stacking many of these blood vessel chips with layers of hepatocytes. The resulting device could basically handle the amount of blood that is processed by a human in a single day.

    - So far, this device has been designed to function more like a dialysis instrument than a replacement organ. But there's a good chance that we will be able to engineer some kind of coating so that the device could be implanted into patients without risk of rejection by the body's immune system.

    - One way to get around the compatibility problem would be to use a portion of a recipient's damaged organ to begin growing a new organ. This has been done for some simpler organs, such as the bladder, and the transplants of these semi-synthetic organs have been successful.

Biology and Medicine Transformed

- As we've seen, the fields of biology and medicine are being transformed by increases in our ability to understand biology and intervene at the nanoscale level. The fact that biology operates at the nanoscale, with tiny messenger molecules carrying out all the work of cells and giving cells clues about how to grow, means that working at the nanoscale is quite important.

- We now have materials that allow cells to grow with defined orientations and allow them to assemble into the kinds of complex structures that are found in humans. We've also seen other advances in nanomedicine, such as improved drug delivery, earlier disease diagnosis, and better tools for surgery. These are materials that simply did not exist before nanotechnology enabled us to manipulate matter at such a fine length scale.

Suggested Reading

Atala, Lanza, Thomson, and Nerem, *Principles of Regenerative Medicine*.

Dvir, Timko, Kohane, and Langer, "Nanotechnological Strategies for Engineering Complex Tissue."

Pearson, "Being Bob Langer."

Webber, Kessler, and Stupp, "Emerging Peptide Nanomedicine to Regenerate Tissues and Organs."

Questions to Consider

1. Why do we need regenerative medicine? Cells know how to grow—why is there a pressing need for nanomaterials to help them along?

2. What health problems could be eliminated once routine *de novo* organ fabrication is available?

How Nano Research Gets Done

Lecture 16

This lecture is devoted to discussing the research process in nanotechnology—the kinds of people that are involved in this research, how it's funded, and how discoveries are moved out of the laboratory and into commercial products. There are thousands of academic labs across the world that are working on nanotechnology-related projects, and hundreds more research labs at companies, in the government, and at research institutes. This is a large community of people, all working toward realizing the applications of nanotechnology that we've discussed in this course.

Interdisciplinary Teams

- The teams that perform nanotechnology research are highly interdisciplinary. In order to move projects forward, it's often necessary to have people with backgrounds in chemistry, physics, biology, and engineering.

- Researchers join these teams at a variety of levels: Some are graduate students, some are postdoctoral researchers, and some are research associates who hold undergraduate degrees.

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People with backgrounds in almost any area of basic science—chemistry, biology, physics—can find a place on a nanotechnology research team.

- On a project at the University of Toronto that focuses on the development of a new type of DNA-modified quantum dot, the project lead is a chemist, who works closely with a master's level student in engineering physics. Students and researchers with backgrounds in mechanical

engineering, biochemistry, biology, and chemistry also contribute to the project.

- Team members in nanotechnology research must be versatile and constantly willing to learn aspects of many different fields that may be involved in a particular project.

Research Funding

- Funding for nanotechnology projects comes from a variety of sources: the government, private foundations, and companies.

- A healthy budget for a group of 20 researchers is about $1 million a year; this money is split fairly evenly between personnel costs and supplies and equipment. Nanotechnology research is a bit more expensive than other types of scientific research because the equipment needed is sophisticated and the teams tend to require many different types of expertise.

- Such organizations as the National Institutes of Health, the National Science Foundation, and the Department of Defense provide research funding.
    - In order to obtain this funding, teams prepare detailed proposals describing their projects that are then subject to rigorous peer review.

    - It's not uncommon for a proposal to be turned down several times before it is funded, but the system works in that it prioritizes high-quality, high-impact research.

Dissemination of Results

- Research results are disseminated in a number of ways, such as by publishing papers, applying for patents, or reporting on results at conferences.

- If the research is basic in nature, such as work done to develop a new material or imaging technique, the outcomes may take quite some time to materialize. Basic research serves as the foundation for

work focused on different applications. For this reason, follow-up work is often needed before new materials can be commercialized.

- Still, basic research is often where game-changing discoveries are made because it is usually curiosity-driven and can take a project in unexpected directions. For example, a project that started as an exploration of the properties of some basic materials based on peptides has led to the engineering of these materials as powerful drug delivery agents.

- With applied nanotechnology research, patents may be generated from the work, and an existing company may be interested in licensing these patents.
    - This company would turn the research into a product, and once it's commercialized, the company would pay royalties to the inventors and the university where the patents were generated. This is the typical process that takes place when new drugs are created.

    - For certain types of inventions, it may make more sense for a new company to be created—a spin-off or start-up. This approach is often used in creating new technology, because the kind of work required to mature a technology to the commercialization stage cannot usually be done in a university lab.

    - One of the best funding channels for start-ups based on nanotechnology research is venture capital. The advantage of giving venture capitalists equity in a company in return for an investment is that in addition to getting funding, the company also gets access to the contacts and experience of the investors.

A Case Study in Commercialization

- As mentioned earlier in the course, colloidal quantum dots represent an exciting development in nanomaterials. These materials can be synthesized in solution, essentially making a

paintable semiconductor, and they can be tuned—customized to certain applications.

- Devices made with colloidal quantum dots are extremely good photodetectors, and the dots themselves can be engineered to see in the infrared. Thus, they offer the potential to create an image sensor with capabilities that go far beyond conventional imaging.

- In 2005–2006, the company InVisage was formed to commercialize these very sensitive photodetectors. Since that time, the company has built prototypes that improve the capability of these materials to enhance the sensitivity of image sensors in cell phones.

- New functions have also been incorporated into these chips. For example, a true electronic shutter has been developed that eliminates the jitter present in cameras.

- Although it seems as if working with these remarkable materials and exotic ideas might translate into high costs, it's possible to achieve low cost and high performance simultaneously with nanomaterials.

- It's also true that commercialization offers the possibility of marrying new developments with established technologies. In the case of InVisage, the firm has combined a new light-sensing capability with a platform of microelectronics that is cost-effective and manufacturable.

Research Leaders in Nanoscience

- Paul Weiss is the director of the California NanoSystems Institute. His work is involved with gaining an atom-scale understanding and control over the properties of materials, and he is quite talented in the use of scanning tunneling microscopes.
    - Weiss insists that science gets interesting when he's exploring the ground rules of phenomena that are distinct as a result of being at the nanoscale.

- In addition to directing a large program, Weiss also founded a journal for the dissemination of nanotechnology research, *ACS Nano*. The journal has been active in disseminating research through social media and in attracting contributions from top scientists in the field.

- John Polanyi is a professor at the University of Toronto and winner of a Nobel Prize in 1986 for his work in the field of reaction dynamics, which looks to understand how chemical reactions occur. In particular, Polanyi advanced the method of infrared chemiluminescence, enabling people to see the energy coming out of chemical reactions in real time.
  - Polanyi is now working in surface-aligned photochemistry, studying the chemical reactions that result from the interactions of molecules at specific angles.

  - In addition, Polanyi is what we might call a scientist for peace. He has spoken out internationally on such topics as nuclear armaments and nuclear energy. He seems to believe that scientists should use their deep understanding of technical issues to address important questions in public policy.

- Michael Graetzel is a professor at the École Polytechnique Fédérale de Lausanne in Switzerland and is acknowledged as the inventor of the first efficient dye-sensitized solar cells, essentially the first solar cells that showed promise for being very low in cost. Like the other scientists mentioned here, Graetzel is distinguished on the world stage, yet he continues to study every element of the system that he invented and teams with other researchers around the world.

Corporate Research Activity

- A great deal of exciting research activity is also performed in the corporate world. A group at DuPont, for example, published a prestigious paper on sorting carbon nanotubes with the aid of DNA. This work had a direct impact on DuPont's realization of flexible substrates for photovoltaics, enabling the printing of solar cells based on roll-to-roll processing.

- Researchers at IBM developed the scanning tunneling microscope and have done important work on carbon nanotubes and graphene in the context of electronics. The company has recently shown some striking results in integrating these new classes of materials onto silicon. IBM has also shown leadership in the field of photovoltaics, with researchers looking at Earth-abundant materials that can be turned into energy-harvesting materials.

- Researchers at Intel have done work on figuring out how to wrap the gate electrode around the channel of a transistor in order to allow scaling to smaller dimensions. In fact, Intel has always been very much in the lead in downward scaling.

- Research and the transformation of research into products can be thought of as an ecosystem, and it's because of the existence of this ecosystem that nanotechnology is having a growing impact on our lives every day.

Suggested Reading

Christensen, *The Innovator's Dilemma*.

DuPont, "Science and Technology at DuPont."

IBM, "IBM Research."

Intel, "Intel Labs Research Areas Overview."

InVisage, "Technology."

Mouttet, "Nanotechnology and U.S. Patents."

Questions to Consider

1. What challenges related to bringing a product to market are specific to nanotechnology, as opposed to being general to all technology commercialization endeavors?

2. Everything is made from atoms and molecules, yet not every product is a nanotechnology innovation. How would you define a nanotechnology product?

Nanomotifs—Building Blocks, Complex Structures

Lecture 17

Throughout much of this course, we've concerned ourselves with nanotechnology from the point of view of its applications, but it's also fascinating to view nanotechnology through the lens of design or architecture. In this lecture, we'll look at the incredibly diverse building blocks of nanotechnology and the capability of crystal facet engineering these building blocks give us to create beautiful structures.

Building Blocks of Nanostructures

- A nanoparticle is approximately a sphere, but because such particles are crystalline arrays, they possess facets. The constructions we build on top of nanoparticles are called core shell structures.

- The term "epitaxy" is used to describe the growth of crystals on top of other crystals. The key to this term is the idea that the spacing among the atoms in the first material is perfectly mimicked in the second material that lies on top of it.

- The term "heteroepitaxy" is used to describe the growth of a shell of a second type of material on top of a first material. Such heteroepitaxial core-shell nanoparticles have properties that go well beyond those that are embedded in the cores alone.
    - We've already discussed the fact that we can change quantum confinement at the core. We can also wrap a core within a shell to achieve a decrease in the degree of overlap between more and less excited energy states.

    - As a result, the transitions that occur within a core-shell nanoparticle can be different. If the overlaps are weak between the two states—the initial and the final state—we'll have a weak transition, and we may have poor luminescence from the materials. If we engineer a shell that's efficient at cramming

the electron and all of its possible states tightly inside the core, we can achieve a much more strongly luminescent structure.

- This is an example of what can be accomplished by engineering on just one more length scale beyond the core itself. In fact, we can build structures that embed many layers of shells, in which each of those layers is used to manipulate the structure of the material within.

Crystal Facet Engineering

- As we said, a nanoparticle is approximately spherical, but it still has facets, regions where certain atoms of 1 type are exposed and others where certain atoms of another type are exposed.

- As an example, let's consider a binary material that consists of tin and sulfur. If we were to slice it along certain axes, we could see tin and sulfur atoms in equal ratios, 1:1. There are other axes on which we could slice it where we would see only tin atoms or axes where we would see only sulfur atoms.

- We can engineer the propensity for these facets to react and, thus, differentiate certain facets from others. For example, we might want to grow an "arm" off 1 facet while protecting the other facets that don't have the same degree of reactivity. The ability to control these facets leads to the capacity to build things that are directional.
  - Quantum dots can be thought of as 3-dimensionally confined systems, in which electrons are confined in both horizontal planes and the vertical plane. They can also be thought of as 0-dimensional from the point of view of the number of dimensions on which the electronic states are extended.

  - We can use that same concept to talk of materials that extend the electron along 1 axis but confine it along 2. These we call 1-dimensional materials, where there's a propagation in 1 direction.

- We also have what are called quantum wells, where the electron can swim around freely within the plane and is confined along only 1 axis.

- Nanotubes, rolled up sheets of graphene, allow propagation along their axis and confinement in the other 2 dimensions. If we unroll a carbon nanotube, we produce a graphene sheet. Electrons can skirt around within the plane, but because they are confined to reside within that plane, they function more like quantum wells.

- The traditional inorganic semiconductor materials, such as silicon and germanium, with which we are able to grow various types of nanoparticles, and the carbon-based organic materials, such as buckyballs, nanotubes, and graphene, all have analogs of one another. They all can see different degrees of confinement and propagation engineered at the nanoscale.

Supercrystals and Superlattices

- The easiest kind of structure we could build with nanoparticles would be another crystal. We might think of it as a supercrystal, a periodic array of nanoparticles, in which each nanoparticle is itself internally a crystal.

- To make a perfectly ordered structure of nanoparticles—a perfectly regular array—all the building blocks must be the same. This property is known as monodispersity.

- The other ingredient needed to build a supercrystal is a strategy to allow every constituent nanoparticle to find its place in the lattice. This typically involves a slow growth, similar to allowing a solution of salt and water to evaporate slowly to give every atom time to find its place in the resulting crystal.

- Superlattices can be made not just out of a single particle but from multiple types of particles. This tiling idea has led to binary

superlattices, which allow the fusing of the properties of their constituents and the development of super-semiconductor materials.

- The ideas of oriented attachment have been extended beyond making 3-dimensional crystals to attaching nanoparticles along a 1-dimensional axis to form a string. These long wires are prone to carry electronic charge along their length, while still maintaining quantum confinement along the direction that's perpendicular to the length axis of the wire.

Tetrapods

- A tetrapod is a structure that has a number of legs pointing downward and 1 arm pointing upward. Electron propagation is achieved along the component that points upward.

- This is a useful architecture. The problem with wires on their own is that they are naturally prone to lie down on a surface. The fact that tetrapods plant their legs on the surface and point an extension upward means that they have conduction in the vertical direction.

- To build these structures, crystals that form pyramidal structures are used. The 4 exposed facets are all equally prone toward growth. Thus, we can create 4 substrates at various angles to one another, off of which growth of the rods can occur. Typically, 1 material is used to form the body and another forms the basis for the arms.

- These materials have applications in making more controlled electronic structures. We can combine materials into a single nanoparticle, enabling the inclusion of a metal and a semiconductor, for example. We're also able to create a sense of orientation or a polarization, a propensity for charge to flow in a certain direction.

From Building Blocks to Architectures

- The fact that DNA acts as a powerful type of Velcro® offers a technique for the controllable construction of structures that combine many different nanomaterials.

- One simple structure involves a series of nanowires that are grown from the bottom up. Attached to the nanowires are single-stranded pieces of DNA. In a separate reaction vessel are nanoparticles with complementary strands of DNA attached. The fusing of these two different classes of nanostructures forms a new nanostructured material.

- This concept leads to the idea of combining nanoparticle types with different colors. Each of these could be labeled with a different sequence of DNA, and the number of DNA strands that would adhere to each could be controlled.
    - The DNA concept, putting a programmable number of strands on a surface, is analogous to the valency idea in the periodic table. We could start with a large inner nanoparticle, having, say, 4 pieces of DNA on it that displayed a certain sequence. We could then couple that to a green class of nanoparticles having the complementary sequence and, thus, ensure that the center nanoparticle had exactly 4 green nanoparticles bound to it.

    - Extending this idea even further, a third class of nanoparticles could be introduced that would bind to the second class. In this way, crosses and triangular structures could be built from an inner-core nanoparticle.

    - With this process, nanostructured materials could be designed in a controlled fashion by simply combining ingredients.

- In research at the University of Toronto, we used this process to build a structure in which the outermost set of nanoparticles possessed excited electrons when it was illuminated at the highest available energy state; the inner ring had a sort of middling energy excited-state level; and the heart of the structure had the lowest energy.
    - When we photoexcited the outer ring, energy was inclined to trickle downhill; the energy would pour into the inner shell, then to the center nanoparticle. We built, in essence, an energy

funnel. We could have an absorption from this complex that was proportional to the number of nanoparticles.

- This funnel is an analogy to the way in which the photosynthetic apparatus acts in plants. Plants have evolved systems that function like antennae to harvest light. They actually extend their reach for light absorption and then funnel energy down toward a reaction center.

- We did the same thing with our multi–length scale structured molecular complexes, and we showed that the efficiency with which we were able to capture and transfer energy toward the virtual reaction center was extremely high.

- Interestingly, we were also able to turn this phenomenon on and off by changing the pH within the structures or within the solution.

Virus-Shaped Nanoparticles

- Angela Belcher at MIT is working to merge the world of the biological with the world of nanoparticles. She has been able to engineer materials that take on the shape of viruses by growing semiconductor nanoparticles off the surfaces of viruses.

- Belcher has further combined the field of semiconductors and material science with the field of genetic engineering in that she's been able to find which proteins displayed on the surface of these viruses allow growth with particular success, that is, with particularly high yields of nanostructured materials.

- This work illustrates the idea that when we think about nanomotifs, we don't have to limit ourselves to thinking only about inorganic semiconductors or only about organic materials; we can get biological entities and even life forms into the game for engineering on many length scales.

Suggested Reading

Lee, Mao, Flynn, and Belcher, "Ordering of Quantum Dots Using Genetically Engineered Viruses."

Ozin and Arsenault, *Nanochemistry*.

Whaley, et al., "Selection of Peptides with Semiconductor Binding Specificity for Directed Nanocrystal Assembly."

Questions to Consider

1. The existence and structures of many types of matter were hypothesized before direct observations were made. Why was it difficult for us to even imagine that such structures as carbon nanotubes and fullerenes (buckyballs) existed before they were characterized?

2. Are there any limitations we can envision for the structures of nanomaterials? Should there be an infinite or discrete number of nanomaterials?

Using Nanotechnology to Capture Sunlight

Lecture 18

So far in this course, we've spoken about nanotechnology in relation to information and communication technologies, as well as biology and medicine. But if we think about the biggest challenges facing the world today, another one that immediately comes to mind is energy. How can we capture and store renewable, sustainable, and clean energy? In this first lecture of a series on energy, we'll look at the role of nanotechnology in harnessing and using solar energy.

The Sun and Its Properties

- As you're aware, on the spectrum, the Sun is very hot. That explains the fact that the peak of its emission lies within the visible spectrum. In addition, however, the Sun has a significant spectral signature in the low-energy infrared and near infrared. Opportunity for making more efficient solar cells can be found in making full use of the Sun's broad spectrum.

- Note that the Sun is the opposite of a laser. If it were a laser, we'd have an easier time making solar cells because we could tailor our converters of light energy to 1 specific wavelength.

- It's not true that Earth does not receive sufficient energy from the Sun to meet a significant portion of our energy needs. The total amount of energy reaching the Earth every hour from the Sun is, in fact, enough to meet the world's energy needs for a year. The reason we haven't made fuller use of the solar resource is that we haven't yet found ways to make solar cells that are simultaneously efficient and low cost.

1st- and 2nd-Generation Solar Cells

- Flexible solar cells offer the promise of significant cost reductions as a result of their ease of fabrication. Because they aren't rigid, they can

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A significant part of the cost of solar cells—and the impetus for application of nanotechnology to the enhancement of solar cells—is rooftop installation and maintenance.

be made using roll-to-roll processing, similar to the way a newspaper is printed. The flexibility of these cells also facilitates deployment.

- Silicon-based solar cells have their own version of Moore's law, a rate of improvement in the efficiency-to-cost ratio. In this case, the law predicts that it will be many decades before we will be able to transform conventional existing solar technologies into compellingly cost-effective technologies.

- What we need is a new regime, something that will steer us away from merely extrapolative improvement in solar cell efficiency. Neither the 1st generation of solar cells—silicon solar cells—nor the 2nd generation—flexible solar cells—has led to breakthrough improvements in efficiency combined with reductions in cost.

- The opportunity for the 3rd generation of solar cells is to make such better use of the Sun's broad spectrum that we can

overcome the limitations of using a solar cell based on a single semiconductor junction.

Absorption inside a Semiconductor

- As we've discussed, when an atom, such as a silicon atom, exists in isolation, it has shells that correspond to the energetic levels that electrons fill up. That accounts for silicon's membership in a particular column of the periodic table. These shells are called discrete energy levels. They are well defined and distinct—only certain energetic transitions are available through each type of atom.

- In a semiconductor material, the behavior of the constituent atoms doesn't matter; what matters is what happens when they come together. When these atoms come together, electrons have some extent; they start to merge and exist over many atoms.
  - Inside a semiconductor, this phenomenon is advantageous. The fact that electrons can propagate as waves along a semiconductor is the basis for good electronic transport.

  - It also leads to the establishment of energy bands. Instead of having discrete steps, there are now ranges of energy where electrons can exist and propagate freely. In between energy bands are chasms that are called band gaps.

- In building a solar cell, the band gap of the semiconductor must match the spectral properties of the Sun reaching the Earth. Silicon has a band gap that is actually very well matched to the emission properties of the Sun.

- It's worth noting that the light sensors we spoke about in an earlier lecture and solar cells have quite a bit in common. Each is responsible for absorbing light, and each typically covers the visible and a bit into the near-infrared wavelengths.

  - Solar cells, however, must work with a preordained intensity—1 sun, the unit of intensity used to describe the brightness of the

Sun. Light sensors typically deal with intensities that are much, much lower.

- Further, sensors convert information about the physical world into an electronic representation. That means it's acceptable to put a bit of potential across the photodetector. But in solar cells, the goal is to harvest energy—not expend it. We want the device to deliver the Sun's photons to us in the form of an electrical current. Thus, the mode of operation of photovoltaic devices and solar cells is different.

The Heart of a Solar Cell

- In building a solar cell, two materials are brought together that have the same semiconductor band gap but are dissimilar in their affinity for electrons. One of these materials will be rich in electrons, and on the other side of the junction, the other material will be depleted of electrons.

- When we excite a charge on one side of the junction, we now have a propensity for the electrons to go from one side to the other as a result of this built-in cascade, or potential. That asymmetry is one of the crucial conceptual building blocks of any solar cell, because it doesn't involve applying an external electrical bias. The device is one that absorbs light, then funnels the energy that's extracted from that light in a specific direction toward a circuit.

- The existence of the semiconductor band gap means that there will be certain photon energies below which there is no absorption in the semiconductor; these colors of light will simply pass through the solar cell. Others will just barely cross the band gap, leading to absorption. In fact, this is a very efficient region of the spectrum for solar cells because all of the energy in the photon that impinged on the semiconductor is extracted.
  - As we've said, however, the Sun's spectrum is broad, and there are photons at much shorter wavelengths corresponding to much higher energies where there's an overabundance of energy in each photon.

- If we could harvest that entire photon energy, we'd be doing well, but the way semiconductors work is that if we excite an electron well into a band, it trickles down to the band edge extremely rapidly.

- Further, the states within a given band are very well coupled to each other. Thus, at room temperature, we get a rapid loss of energy; photon energy is converted into thermal energy, not something we can harvest inside a photovoltaic device.

- This idea of loss of energy from a given photon is important in understanding the limits on solar cell efficiency. If we were to use a semiconductor with a larger band gap, we'd be able to extract more power, but it would also absorb fewer photons because there would be more photons in the Sun's spectrum that would not be able to breach the band gap.
  - This leads to the choice of a semiconductor band gap that is small enough to enable the harvesting of a good fraction of the Sun's photons but large enough that we don't throw away too much energy.

  - A photovoltaic device based on a single band gap achieves a power conversion efficiency of only about 30%.

Using Nanoscience to Improve Efficiency

- One of the concepts of nanoscience applied to make solar cells more efficient involves a textured solar cell.

- As we've said, silicon is a good absorber of blue photons (the more energetic, visible photons), but it gets much weaker in its absorption of light at longer wavelengths, even those above its band gap. Thus, silicon is called an indirect band gap semiconductor.

- When we try to make an efficient solar cell, we're trying to absorb all of the light across the Sun's spectral region that is above the band gap. With silicon, it's necessary to make a very thick wafer of semiconductor in order to absorb all of the light in the infrared

because of silicon's weak optical absorption in the infrared wavelengths. Historically, this has driven up the cost of silicon solar cells.

- But if we roughen the surface of a silicon solar cell, we create the opportunity for multiple passes through this device. Instead of bouncing in and out of the solar cell and losing its chance for absorption, light is typically reflected or scattered in a different direction by the rough surface.

- This phenomenon in which light is trapped inside a semiconductor and given multiple opportunities to bounce around is called light trapping, and there are now low-cost and convenient methods to make nanostructured silicon surfaces that are prone to trapping light.

Suggested Reading

Green, Emery, Hishikawa, and Warta, "Solar Cell Efficiency Tables."

Nelson, *The Physics of Solar Cells*.

Sargent, "Infrared Photovoltaics Made by Solution Processing."

Questions to Consider

1. How abundant is the element silicon? In light of this, what drives the cost of silicon solar cells?

2. How do the time-of-day cycles of the Sun's power incident on a given site on Earth compare with the cycles of our energy consumption? What are the implications of these cycles and their partial alignment on our willingness to pay for solar energy compared to coal-fired plant electricity? What do they mean for the importance of energy transport among jurisdictions in different time zones and climactic zones? What do they mean for the importance of, and our willingness to pay for, electrical energy storage?

Photons to Electricity—Nano-Based Solar Cells

Lecture 19

This lecture continues our exploration of the fascinating ways in which nanotechnology can be used to make solar cells that are more efficient and more cost effective. Here, we'll look at plasmonics, tandem- and triple-junction solar cells, solar cells made with organic materials and with colloidal quantum dots, and dye-sensitized solar cells that use dye to achieve light absorption.

Plasmonics

- In an earlier lecture, we saw that plasmonics provided a convenient method for conveying optical information and confining light to very small regions. The basis for this was small particles of metal that act like stepping stones across a pond or a river for electromagnetic waves.

- If you're the river in this conception, those stones look like scattering centers. In photovoltaics, there's an emerging effort to use metal nanoparticles—plasmonic particles—to scatter light in various directions, similar to the function achieved with light trapping.

- Nanotechnologists know very well how to synthesize metal nanoparticles dispersed in solution into paintable materials and simply coat them onto things. This provides a ready means of making devices that have a greater capacity to enhance the absorption of light using nanoscale interactions between light and, in this case, metals.

Tandem- and Triple-Junction Solar Cells

- In the last lecture, we spoke about the limitations of solar cells that have a single junction. One obvious solution is to make a semiconductor device that has many different band gaps. In fact, before the advent of the latest solution process approaches, there was much work on tandem- and triple-junction solar cells.

- Semiconductors with different band gaps were grown on top of one another. These cells offered an advantage in terms of efficiency because they allowed a 1st cell, with a large band gap, to harvest the visible portion of the Sun's spectrum in a way that provided a good deal of voltage. Then, they stepped down to an intermediate band gap layer and a small band gap layer. These produced lower voltages, using the photons that made it through the visible band gap cell.

- The design of these devices was complicated by the need to ensure that the current generated within each layer is the same (current matching). The design of traditional triple-junction devices had an added complication: the fact that different materials have different lattice constants, the characteristic spacing among the atoms. If each material is to be a perfect crystal, then how can they be integrated with one another without slips?
    - The answer is that they can't, resulting in places where the solar cell loses efficiency or reliability.

    - In making these stacked solar cells, researchers were forced to come up with even more complex material combinations, using 3 or 4 constituent atoms in very specific ratios. This approach leads to costly solar cells.

    - Such costly cells have a place in concentrated photovoltaics, where optical methods are used to focus light from the Sun onto very small solar cells. However, the lenses for focusing inside these devices add to the cost, as does the need to ensure the cells track the Sun over the course of the day.

Organic Solar Cells

- The field of organic photovoltaics seeks to marry some of the desirable properties of organic materials with the urgent need to make cost-effective solar cells. One of the obvious advantages of using an organic approach would be in making solar cells that are physically flexible.

- The synthesis of organic molecules is well developed. Those who work in synthetic organic chemistry know how to make a broad swath of molecules designed to achieve the precise functions desired in photovoltaics.

- In organic photovoltaics, the twin goals are strong absorption and conduction of energy, but organic molecules are traditionally thought of as insulators, not conductors.
  - Researchers have found ways to use the bonds they can engineer along chains of polymers to achieve delocalization of electrons; electrons can be everywhere along these chains.

  - Essentially, this is a way to replicate the good qualities of semiconductors in an organic system and a powerful platform for thinking about how to make low-cost solar cells.

- The other component of making a good solar cell is to think about the way it utilizes the Sun's spectrum. There are some advantages to the organics on this front, as well.
  - In particular, researchers are able to design and define the optical resonances of these materials to lie somewhere in between the properties of individual atoms and the properties of semiconductors.

  - As a consequence, there is an extremely strong absorption of light in these designer molecules, which means that a very thin layer of these materials can still achieve complete absorption of light.

- The fact that this absorption is concentrated into a rather narrow band implies that we are not necessarily addressing the Sun's full spectrum. But that can be achieved through mixing semiconductors that have different properties—through the realization of tandem- and triple-junction solar cells. Each layer in these cells consists of a different organic molecule, each tailored to managing a particular portion of the Sun's spectrum.

The Donor-Acceptor Junction

- The concept at work in organic photovoltaics that was quite distinctive when it was first introduced is the donor-acceptor junction.

- As we saw, a device can be made out of a single type of semiconductor having 2 different types of impurities: an electron richness and an electron impoverished quality.

- Organic molecules tend not to be rich in free electrons, but the energy levels in 2 different molecules can be matched up such that there is an asymmetry. The electrons generated in a 1st class of molecules known as the donor can be efficiently donated to an adjacent molecule that functions as the acceptor.

- Essentially, when light comes into these solar cells, it generates an exciton—an excited particle—and that particle is split apart and pulled into the acceptor molecules, giving it a much longer lifetime for extraction.

- The reason it's important to extract these energetic charge carriers efficiently in organic solar cells is that the transport properties—the mobilities—of electrons inside these materials are much lower than in perfectly regular semiconductors. It's thus necessary to find a way station for these excited charge carriers rather than have their energy disappear before the charges can be extracted.

- Researchers have made naturally interpenetrating fingers of donor and acceptor material to enhance the absorption of light and to ensure that energetically favorable interfaces are readily available for the extraction of charge carriers. Further, work has been done to enable these cells to continually extract electrons into the acceptor without producing islands, that is, isolated regions where electrons can't be extracted.

- In donor-acceptor junctions, one of the stars of the show is the buckyball. This molecule, which looks like a soccer ball, participates in the light absorption and extraction process.

Collodial Quantum Dot Solar Cells

- As we've seen in earlier lectures, quantum dots are semiconductor particles that have a band structure we can tune or define through the quantum size effect. In the context of solar cells, that spectral tunability enables us to change whether these particles absorb visible or infrared light.

- With tandem solar cells, we had to find ways to match their lattices—the spacing of their atoms—which led to increased costs. With quantum dot solar cells, we are able to choose the band gaps through the quantum size effect.

- In working with semiconductor nanoparticles, we don't have to confine ourselves to quantum dots; we can also make elongated structures—rods—in which there is a clear preference for flow along the long axis. This is a perfect semiconductor crystal that's compatible with the delocalization of electrons along its length. These materials have attracted great interest because of their enhanced electronic transport properties.

- Coupling nanoparticles together and packing them into a superlattice shows promise for achieving the progress needed to make colloidal quantum dot solar cells highly efficient. These lattices have multiple length scales, each of which is important. The smaller length scale achieves the desired semiconductor and transport properties, while the larger one allows the propagation of electrons.

Dye-sensitized Solar Cells

- Dye-sensitized solar cells achieve light absorption using a dye, such as what you'd find in food coloring. These molecules are very good at absorbing light, but on their own, they are not conductors. The dyes must be put on essentially a sponge of semiconductor that is good at transporting electrons.

- The surface area of the sponge ensures that every pigment is in immediate proximity to an electron acceptor that can extract the electrons. This concept is similar to the interpenetration of materials

we saw in the organic solar cells. Both ideas take advantage of our capacity to maximize surface areas for beneficial effects in engineering nanomaterials.

- Some of these exciting new technologies are being commercialized, and some of their commercial applications are taking advantage of the attractive properties of physically flexible materials. We can go beyond just thinking about installing these materials on rooftops or integrating them into building materials to imagining solar backpacks or tents or mobile phones in which we're able to achieve energy harvesting.

Suggested Reading

Green, Emery, Hishikawa, and Warta, "Solar Cell Efficiency Tables."

Nelson, *The Physics of Solar Cells*.

Sargent, "Infrared Photovoltaics Made by Solution Processing."

Questions to Consider

1. Nanoparticles are small, yet solar cells must be large. What advantages do nanomaterials offer in solar energy harvesting, and what new challenges do they present?

2. What are the advantages and disadvantages of a solar cell that, like dye-sensitized cells, requires the use of a liquid electrolyte to make one of the key electrical connections inside the solar cell?

Nanotechnology for Storing Energy

Lecture 20

We've spoken about harvesting energy from the Sun, but another essential part of managing energy, especially renewable energy, is storing it. In this lecture, we'll talk about how nanotechnology is enabling us to advance and enhance the storage of energy. We'll discuss the use of nanomaterials to improve the density of energy storage, and we'll look at some novel concepts for energy storage, such as ways of using viruses to assemble new styles of batteries.

Harvesting versus Storing Energy

- In the future, we anticipate that a much larger fraction of our energy budget will come from renewable energies, such as solar or wind energy. But of course, one of the challenges these renewable energy forms present is that we can't turn them on and off. Further, the time-of-day variations in the Sun require a buffer to map to our energy needs.

- A new concept has emerged recently in the management of energy known as the smart grid.
  - This idea recognizes that the traditional power distribution network is based on a unidirectional flow of energy: a small number of large, centralized power-generating stations that spread energy out toward the consumer.

  - With renewable energy, however, consumers are also producing energy and may sometimes produce more than they need. Consumers may wish to sell their excess energy, which means that the grid becomes 2-dimensional.

  - One of the key elements in building a smart grid that's 2-dimensional and allows the flow of energy in a managed fashion is energy storage.

- Our challenges on the energy storage front may occur on many different scales, from the battery packs inside our laptops to the storage of energy needed to run a community.
    - In addition to batteries, fuel cells represent another strategy for storing energy. In a battery, the means of energy storage and replay are integrated with one another, but in a fuel cell, they are decoupled. The fuel, such as hydrogen or ethanol, is separate from the cell, which takes in energy and replays it.

    - Depending on the scale we're interested in and other requirements, such as cost and portability, we may be interested in different systems.

Batteries

- In a battery, there are 2 electrodes; of course, any electrical circuit needs 2 electrodes to complete the circuit. Chemical energy in a battery is typically stored in the form of some kind of anion, such as lithium, in 1 electrode.

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The building blocks of batteries go back a couple of centuries, but today, nanomaterials are enabling increased energy densities inside batteries.

- Playing back that energy and turning it into a current involves the ionic flow through an electrolyte of these ions toward the opposite electrode.
    - In the case of nonrechargeable batteries, that's it; the available energy is expended. The anions flow downhill to release their energy and provide a voltage to a circuit.

    - With rechargeable batteries, we're able to reverse that reaction and drive the anions back to be stored at their original electrode.

But even rechargeable batteries have finite lifetimes; thus, it's important to look at new electrode technologies that enable batteries to have longer usable lifetimes.

- Lithium is a particularly logical metal to use for batteries because it is the most electropositive metal available in the periodic table. That means it gives us the opportunity to develop the largest potential—the largest voltage—which translates directly into energy. It's also the lightest metal, the least massive per anion. As a consequence of those two properties combined, the density of lithium in terms of energy per kilogram can be very high.

- In traditional lithium-ion batteries, the lithium is stored in a graphite electrode, but silicon can also store a large density of lithium ions. Further, exploiting the full energy capacity for storage of lithium within silicon—which is about 10 times the capacity per unit mass that can be stored within graphite—would enable expansion of the volume of the silicon electrode by about 400%.

- Silicon offers this incredible energy density, but it will collapse after a couple of cycles of expansion and contraction. This challenge can be overcome by using nanowires, which can accommodate a good deal of strain without fracture. The silicon nanowires also electrically connect directly to the metallic connector of current. As a result, they don't have isolated regions where their electrons aren't efficiently collected.

Genetic Engineering and Energy Storage

- Some very exciting and creative work has been done at MIT, in which viruses have been used to assemble new classes of batteries. Angela Belcher, whom we discussed in a previous lecture, collaborates in this work with Yet-Ming Chiang.

- One of the ideas behind this work is that a virus can have various genetic options injected into it. Various families or classes of viruses can then grow, and we can use selection approaches to preserve and amplify only the ones that are desired.

- This concept has been used in genetics for some time, but using it in the context of building up inorganic materials—selecting viruses that could, say, build a battery—is a novel approach. Belcher and Chiang were particularly interested in building cobalt oxide, an interesting electrode for new battery technologies.

- There were two stages to building a virus that was coated with cobalt oxide nanoparticles and could then be useful in conduction: (1) put cobalt oxide particles on a surface and (2) make the material more conductive.
    - The researchers first searched for and selected viruses that were particularly prone to attract cobalt and to grow cobalt oxide on their surfaces. Using transmission electron microscopy, they verified that the viruses had a rich coating of cobalt oxide nanoparticles on their surfaces and that these particles were consistent in size.

    - To make these viruses more conductive, the researchers put an additional protein on the surfaces to enable the growth of gold nanoparticles, leading to a dramatic improvement in conductivity.

- Belcher and Chiang also determined the conditions under which they could coat their viruses onto a flexible piece of plastic. By managing the charge on the viral particles, they ensured that the viruses assembled into smooth lamellar structures. Building batteries in this way consumes very small amounts of energy.

Supercapacitors

- Supercapacitors are another paradigm in energy storage, allowing for rapid acceptance, charging, and playback of energy.

- Capacitors are one of the building-block circuit elements that allow us to store a charge. In electrical engineering, we usually think of having 2 plates separated by an insulator; by putting a positive charge on 1 plate, a negative charge is induced on the opposite

plate. With the presentation of a voltage to drive the device, we can release the resulting electrical field in the form of a current.

- With supercapacitors, the goals are to achieve the greatest possible energy density and a long lifetime. Because they are primarily moving electrons around—instead of moving ions around and imparting true chemical changes—supercapacitors can accommodate many more cycles than batteries.

- Researchers at Stanford have been working on making a wearable supercapacitor. In fact, the field of wearable electronics has attracted a great deal of attention and excitement.
    - The idea here is you could collect energy through, perhaps, a flexible solar cell, and you could store that energy for later use.

    - The Stanford group figured out how to incorporate single-walled nanotubes into traditional cotton in such a way that the fabrics themselves were able to store a great deal of charge. Playback was also achieved through tens of thousands of cycles.

Suggested Reading

Aricò, et al., "Nanostructured Materials for Advanced Energy Conversion and Storage Devices."

Ryhänen, Uusitalo, Ikkala, and Kärkkäinen, *Nanotechnologies for Future Mobile Devices*.

Voelcker, "Lithium Batteries Take to the Road."

Questions to Consider

1. What are the most important qualities in a battery used in a mobile device and in a home? Where would you expect nanotechnology to have a greater impact?

2. What are the fundamental physical properties that limit the energy density of a medium—the amount of energy that could ever be stored per unit volume of matter?

Nanotechnology for Releasing Energy

Lecture 21

Our usage of the word "catalyst" in everyday conversation represents a good analogy with how the term is used in science. Just a little injection of something—a surface on which a reaction can occur, a particular shape, a particular angle, a particular availability of electrons—can lead to a rush of chemical activity. In this lecture, we'll see how nanotechnology helps us engineer these reactions toward higher yield and, thus, better use of the input materials, better use of energy, and generation of purer substances as the output.

Catalysis

- A catalyst is something that fosters a reaction without being consumed in the reaction. In a hydrogen fuel cell, stored hydrogen is the fuel. Simply using oxygen from the air, we're able to produce H_2O, a lower-energy molecule. The energy that is extracted in the production is harvested and turned into electrical power. This reaction requires a catalyst.

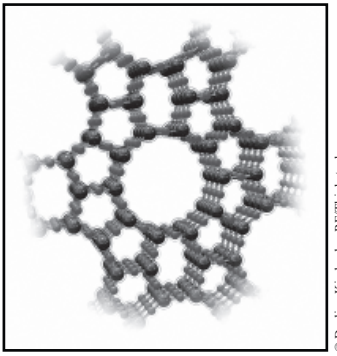
- Platinum is an extremely effective catalyst, and it has been widely used to make fuel cells operate. Of course, cost is a concern in using platinum, as is the phenomenon known as catalyst poisoning, in which the catalysis can no longer be effected after large numbers of uses.

- The idea of a crucible is also important in discussing catalysis. We cannot let reactions that require specific interactions proceed without some kind of surface or tether; otherwise, the interactions between the molecules in the reaction may not take place or they may not take place with the required alignment.
    - With a crucible, we create a surface that attracts one of the molecules that will participate in the reaction and orients those molecules at the right angle such that the second molecule will be exposed to a reactive site.

- In other words, the crucible presents the optimal angle and orientation for causing the reaction to occur.

Zeolites

- Some reactions can be catalyzed simply by planar metal surfaces, but in the nanoworld, templates called zeolites are helping to achieve innovations in catalysis. Instead of being planar, zeolites present a 3-dimensional structure—a kind of complex, like a crystal, but built out of things that look more like molecules.



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Zeolites are catalysts used in the process of hydrocarbon cracking—breaking down heavy hydrocarbons, such as diesel fuel, into lighter ones for use in powering our cars.

- Zeolites are used in the process of converting crude oil to the kinds of fuels we wish to consume. In this process of hydrocarbon cracking, the goal is to break down heavy hydrocarbons into the lighter hydrocarbons that are used as gas in our cars. Here, zeolite is designed to achieve the size and shape that will allow the reactions to proceed that break these longer molecules into shorter, lighter molecules.

- In addition to providing the surfaces for these reactions, zeolites also produce what is called steric hindrance. "Steric" refers to the effects of size. Here, the term is used to refer to the fact that certain molecules will preferentially adsorb inside the tubes that make up the zeolites, or they'll be blocked, or they'll move through them very rapidly or slowly.

- Some specific examples of the zeolites that are used in crude oil–cracking include the aluminosilicates, which combine various aluminum, silicon, and oxygen atoms in order to make rings with defined sizes.

- In the hydrocarbon-cracking process, the heavy hydrocarbons are first brought into contact with the catalyst and combined with elevated temperatures to inject the energy that's needed for the reactions to occur.

- We can think of the zeolites as sort of a molecular sieve. They enable us to achieve size selection and, to some degree, chemical selection based on the structure of the materials that are produced.
    - Chemical interactions on the inner surfaces of these tubules can be managed such that those materials that are smaller or less interactive with the surface are prone to move through quickly, whereas others move more slowly.

    - In this case, the purification provided by the sieve isn't necessarily based just on what does or does not go through. Here, we can drive a solution through the molecular sieve and collect the products on the other side, but what comes out first will be the least interactive or the smallest molecules and what comes out last will be the larger molecules.

    - This sequential purification is attractive because we may have different uses for the different constituents of an impure substance. A similar process is also used in experimental laboratories when we want to remove, say, water from an organic solvent to control the interactions of water and metal. In addition, zeolites can be used to separate molecules into different size categories.

- We can define the chemistry that takes place in all these reactions using the regularity of the zeolites, the symmetry of their pores, their shape, and our knowledge of the chemical reactions required to form these rings. We can think of these pores as forming traps that molecules get stuck in.

- We are also able to gain greater selectivity with zeolites through the way in which we impart energy into the reactions. Rather than imparting energy into the matrix of zeolite, which means that every

molecule participating in the reaction gets some energy, we're able to use laser light to selectively excite only certain classes of molecules inside the reaction.

- This allows us to achieve control of the reaction via position, size of molecules, shape of molecules, and the amount of energy we put in.

- This control, in turn, allows us to create new molecules that we weren't able to build before and to enhance yields, that is, to produce the desired molecule with a higher probability.

- In the process, we consume less source material and less energy, and we generate less waste.

Fuel Storage

- Consider for a moment the properties that would be desirable for hydrogen storage. For an automotive application, we would like to store this fuel in the smallest possible volume. We'd also like to maximize the density of fuel per volume and the ratio of the amount of fuel stored to mass. For applications that involve a stationary storage region, we would focus on minimizing the cost of storage, but the energy density per unit mass might not be as important.

- Metal organic frameworks are particularly attractive in these application areas. Here, metal atoms are bound together using organic molecules; we refer to organic molecules that are particularly prone to bind metal atoms as ligand.
  - A network or framework is created in which metal atoms occur at various apices or vertices, and connectivity is achieved through organic molecules that are inclined to bind selectively to the metals.

  - This structure enables us to achieve an exceptionally high inner surface area where we can control chemical reactivity. In other words, we've engineered structures in which the combination of metal, organics, and architecture enables us to achieve chemical tunability.

- This chemical tunability is a powerful capability in storing hydrogen molecules on the inner surfaces. In contrast to a canister used for storing hydrogen gas—where much of the volume would be occupied by nothingness—these metal organic frameworks are free of dead volume.

- Given that we're using chemical effects to bind the hydrogen molecules onto the inner surfaces of these metal organic frameworks, you might think that the molecules would be irreversibly stuck there. But in fact, we distinguish in this field between the ideas of chemisorption and physisorption.
  - In chemisorption, there is a binding event that forms a strong tether between a molecule and a surface or between 2 molecules.

  - In physisorption, there is a sort of light relaxing of a molecule onto a surface, and the amount of energy associated with this activity is quite small. We do not need an enormous amount of energy to break the bond to, in this case, extract hydrogen fuel from a region of storage.

- How much hydrogen can we store in metal organic frameworks? Can we pack a hydrogen molecule on atoms that are spaced 0.5 nanometer from one another? The metal organic framework is compelling, but it can't overcome the basic personality of hydrogen. There is a particular transition for this gas into the liquid phase, and we can't get beyond that density limit. But we can approach that limit as closely as possible by using the structure, the selectivity, and the chemical reactivity of these interfaces.

Nanotechnology Applied to Energy Challenges

- Having dexterity at the nanoscale gives us many options in energy storage and playback. We're able to control and maximize the surface area of a material in order to maximize the density of energy we can store on it. We're able to ensure optimal angles and orientations for causing reactions to occur, and we can engineer the structure of nanomaterials to leverage steric effects.

- One of the exciting opportunities in these kinds of catalytic efforts is in taking further advantage of optical control—bringing energy into these reactions using light.
    - This represents an exploration of many of the most attractive building blocks of the nanoworld: our ability to poise electrons, atoms, and molecules; take advantage of their interactions with photons; and selectively bring in laser light, like a knife, in order to sever bonds.

    - This kind of control translates into better use of materials and better use of energy toward our purposes.

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Larminie and Dicks, *Fuel Cell Systems Explained*.

Withers, "Fuel Cells: Catalysis on the Cheap."

Questions to Consider

1. In everyday English, the term "catalyze" is commonly used in a manner analogous with its use in energy playback. Where does the analogy fit, and where does it fall apart?

2. What factors limit the rate at which energy can be played back from a stored state?

Energy's Holy Grail—Artificial Photosynthesis

Lecture 22

We've talked so far about capturing the Sun's abundant energy and turning it into electricity. We've also talked about storing that energy. Do we have to think of these things as separate? As we know, plants take energy from the Sun and convert that energy into stored fuel. The dream of artificial photosynthesis, which has made vast progress in recent years, is that we could mimic nature by using sunlight to directly generate fuel.

Photosynthesis

- Photosynthesis is the conversion of carbon dioxide into organic carbons. This process occurs in plants, algae, and many species of bacteria. Organisms that are capable of harvesting energy and creating their own food are called photoautotrophs.

- To make the solar cells that we discussed earlier, we have to invest energy. Photoautotrophs use the energy from the Sun to build themselves. It's wonderful to dream about a photosynthetic apparatus that would build itself without our having to consciously engineer it.

- In photoautotrophs, the chlorophylls that are used in the absorption of light turn photons into energetic electrons, which are then available to participate in reactions. The chlorophylls are part of a membrane, tightly folded into cylindrical

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Nanomaterials and nanotechnology may allow us to realize the dream of artificial photosynthesis—converting energy from the Sun directly into fuel, as plants do.

sheets. These structures are used to fill up the interior of a cell, ultimately giving the membrane a large surface area.

- Chlorophyll is also what gives leaves their green color. Recall from our discussion of solar energy that the Sun finds its peak in the visible spectrum, and green is in the center of that wavelength spectrum.
    - That aligns nicely with the fact that the energy required to drive forward photosynthetic reactions is less than what we can get out of the energies available in the photons coming from the Sun.

    - We have sufficient energy within each photon—within each of these quantum particles—to perform the chemical synthesis that is needed to turn carbon dioxide into organic compounds.

Energy Transfer

- Green pigments are embedded in plants and algae in antenna proteins. The process that occurs inside these reaction centers is known as energy transfer.

- When we think of energy transfer occurring using light, we might think of light being emitted and then absorbed somewhere else.
    - For example, we could convey energy across a room using a laser; that would be energy transfer within the optical domain. Inside the antenna proteins in plants, a virtual photon emission event takes place.

    - Energy has the capability to funnel itself downhill without changing from being an excited electron to a photon to another excited electron. With this downward cascade, the flow of energy can be directed.

    - Earlier, we spoke about nanomaterials that were being engineered to have different sizes and, thus, different energy levels. Wherever we are able to concentrate all the energy from an outer ring of nanoparticles onto a central receptor,

we're doing something similar to what takes place in the photosynthetic reaction apparatus of plants.

Energy Conversion

- The efficiencies plants have in their energy conversion are in the range of 3 to 6%, which is considerably worse than the 40% efficiency range in the best solar cells. Yet the photosynthetic approach is the one that has caught on and dominates our global use of energy because there are no system costs associated with photosynthesis.

- There is so much more solar energy available than we need that we don't need to be perfectionists in efficiency in building a device that will mimic photosynthesis. Such a device would have a large area to receive sunlight. The input into the reaction would be water, and the output would be a splitting of that water into 2 innocuous products: oxygen and hydrogen (the fuel).

- What's nice about these reactions is that they evolve gases; thus, we'll simply be responsible for collecting the hydrogen gas out of this cell and storing it or playing it back directly.

Nanowires and Nanocubes

- Nanowires have been extremely important in making progress toward the vision of artificial photosynthesis because they're capable of conveying electricity in a directional fashion and they have an abundance of surface area. We can even put catalysts on the surface of these materials to ensure that the reactions move forward in the desired direction and with high efficiency.

- Peidong Yang and his group at Lawrence Berkeley National Laboratory have recently done some exciting work involving the use of nanocrystals and part of the catalytic process to pave the way toward artificial photosynthesis.
    - By controlling the facets that are presented in nanocubes, researchers have been able to achieve shape-controlled and

size-controlled metal oxides that have particular promise for artificial photosynthesis applications.

- Yang's group realized that they could put together a stack of materials in which different layers carried out sequentially different reactions, somewhat analogous to the cascade that occurs in the photosynthetic reaction.

- Among the techniques used in building up multi-material stacks is the formation of what's called the Langmuir-Blodgett assembly.
  - Here, we have a bath—a solution filled with molecules. Often, the molecules have a propensity to stick in one direction on a particular surface. Thus, we can dip a substrate into this bath and gradually produce layers of molecules that are consistently oriented at an appropriate angle.

  - The result is a bit like a 2-dimensional array of crystals based not on the traditional organic picture of crystals but on organic molecules that pack themselves into certain regions.

  - Yang's group has used this technique to deposit layers of nanocubes of platinum and cerium oxide on top of a silicon dioxide substrate. The result is two distinct interfaces that enable sequentially catalyzed reactions.

- Yang's bilayer structure is somewhat similar to the tandem solar cells we spoke about in the context of solar energy harvesting.
  - Earlier, we were thinking about how to harvest visible photons and infrared photons in sequence and achieve a total energy output from the solar cell that was the sum of the energies of these inputs.

  - The Berkeley group was able to stack these two reaction systems on top of each other and achieve a similar sequential process for catalysis.

Carbon Nanotubes

- Carbon nanotubes have also played an important role in some of the progress that's been made in artificial photosynthesis. One of the key components of making these devices work is to achieve an oxygen-evolving anode.

- Researchers in Italy, collaborating with an Austrian group, have used multi-walled carbon nanotubes to make a particular style of oxygen-evolving anode. In this case, the device was also a multilayered stack, but it was not just a planar device. The researchers were able to functionalize the surface of the carbon nanotubes, wrapping a variety of organic molecules around them. These molecules had "fingers" that were able to grab the constituents needed to participate in the reaction.

- Instead of building a planar sandwich vertically, these researchers built an analog of that sandwich, but they built it out radially. This approach provides more surface area and more opportunity for interaction.

- It's possible now, using the best transmission electron microscopy techniques, to see the composition of elements in these reactions. We can see spectral signatures through the loss of electrons.

- The nanotubes themselves played a couple of different roles in this work on making oxygen-producing anodes. First, they provided a basis for control over the material morphology. The researchers were able to control the surface, control the binding to that surface, and thus, build the structure they desired. This strategy successfully increased the surface area and provided more opportunities per unit volume to achieve particular reactions.

- Second, through the conductive properties of the nanotubes, the researchers were able to funnel the sequential electron transport to the electrode. Here, they used the fact that the tube was engineered to convey energy in a particular direction and to drive reactions in the perpendicular directions and the radial directions.

Genetic Engineering and Artificial Photosynthesis

- The Belcher group at MIT has also worked on the challenge of making self-assembled materials or devices for water-splitting.

- This group has engineered a virus scaffold allowing the assembly of a virus with two key components: (1) the photosensitizer, the material responsible for absorbing light and converting energy from the optical domain into the form of an excited electron ready to participate in a reaction, and (2) attraction to an iridium oxide cluster that serves as the reaction catalyst.

The Role of Nanotechnology in Energy Harvesting and Storage

- In discussing the role of nanotechnology in energy harvesting and storage, we've integrated a number of concepts embodied in the field.

- One of the broadest of those concepts is simply that nanotechnology is an intrinsically interdisciplinary science. In order to build an artificial photosynthesis system, we need researchers who understand biology, physics, and chemistry, as well as material scientists and engineers.

- Large teams of these experts are working to create devices that mimic what trees and plants have evolved to do over the course of millions of years, but we don't have the luxury of that much time. Our energy challenges require solutions in only the next couple of decades.

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Lewis and Nocera, "Powering the Planet."

Regalado, "Reinventing the Leaf."

U.S. Department of Energy, *Basic Research Needs for Solar Energy Utilization*.

Questions to Consider

1. How is a system that integrates energy capture and storage preferable to one that separates these functions, for example, a solar cell connected to a battery or a fuel cell?

2. How does an integrated capture/storage system compare with the process of leaves capturing the Sun's rays and turning them into stored chemical energy and our then burning these leaves as wood? Consider both efficiency and net environmental impact.

Nanorobots and Nature's Nanomachines

Lecture 23

Throughout this course, we've looked at many kinds of manmade nanomaterials, which might lead you to think of nanotechnology as something humans invented. But the fact is that nature is even better at making nanomaterials than we are! In this lecture, we'll look at a series of natural nanomaterials and nanomachines that are far more advanced than those that have been generated artificially.

Manmade Nanomachines

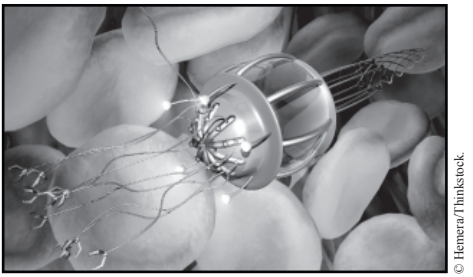
- Typically, a machine converts electrical or chemical energy into another type of energy or force. Movement is one way this conversion is manifested, as we see in cars or sewing machines.

- One simple example of a nanomachine is a nanoscale motor made from a collection of fancy organic molecules. It has different domains that link 2 ends with a chain in between, and then there's a ring threaded onto the structure. When an electron is removed from the complex, this changes the charge on part of the chain, and in response, the ring moves from one site to another.

- Another example of a nanomachine is the nanodragster. This was built at Rice University and uses carbon fullerenes as wheels. The researchers who built this were able to get it to zoom around on a flat substrate, but in order to get the dragster to move, they had to heat it up to about 200° C. There haven't yet been any breakthroughs that allow the nanodragster to power itself like a real car with chemical fuel.

- A nanomachine that can use chemical energy consists of a nanorod that is half platinum and half silver. In a solution of peroxide, this nanorod zooms around like a rocket. What happens here is that the gold portion reacts with the peroxide to generate oxygen, which

then helps the rod to move. A magnetic field can be used to orient the rod and control the direction of travel. This same system can also carry a small cargo around and drop it off at a defined location.



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The size scale of nanomachines means that billions or trillions of them will be needed to perform functions that may be manifested in the macroscopic world.

- Another application of the nanorods involves using them for sensing. Because they speed up in the presence of certain chemicals, tracking their velocity can tell us how much of a certain substance is present. This idea was recently used to detect cancer cells by a group at the University of California in San Diego.

Natural Nanomaterials

- In building nanomachines, one of the concerns is determining what levels of nanomaterials might be harmful to humans or the environment. Such concerns are reasonable, and there are many studies that show we need to be cautious when we scale up the manufacturing of nanomaterials. But it's also true that natural nanomaterials are everywhere in our environment and are not inherently dangerous.

- Among the most abundant natural nanomaterials are diatoms, a type of unicellular algae that are basically everywhere. They handle almost half of the recycling of carbon dioxide into organic molecules and are also an important part of the food chain.
  - There are more than 16,000 species of diatoms, and they come in all shapes and sizes. They also have a fascinating structural feature—an intricately detailed shell made of silicon.

- Diatoms take in silicon from the environment in a soluble form. Once it's inside their cells, the diatoms put the silicon into tiny vesicles with various shapes. The presence of other molecules then causes the silicon to form a nanoparticle, which is transported to the surface of the diatom to build its shell.

- Diatoms are just single cells, so they divide in order to reproduce. What happens here is that 2 cells are made inside of the silicon capsules, and as they grow, they push the halves of the shell apart. Eventually, the parts of the shell separate, and each diatom grows the part that is missing.

- Nanotechnology researchers are dreaming up ways to use diatoms for different applications. For example, a group of researchers in Oregon figured out how to substitute titanium for the silicon in diatoms, which may be useful for hydrogen production or solar energy conversion.

- Certain types of bacteria produce magnetic nanoparticles and keep them within their cells. It's not completely clear what the bacteria use the magnets for, but the presence of the particles means that the bacteria are always aligned with the magnetic fields that surround the Earth. Birds have a more obvious use for magnetic particles; they use internal magnets to help them navigate when they're migrating.
  - The magnetic particles found in birds and bacteria are made of magnetite, a common material composed of iron and oxygen. In nature, the magnetite particles probably get made in the same way as the silicon nanoparticles in diatoms: The iron is processed inside a vesicle and a particle is formed.

  - Homing pigeons have a set of 3 neurons that have magnetite particles within them. We don't know how birds transduce the information coming from these particles, but we do know that the magnetic particles help them figure out whether they're pointing north or south. Birds may also use this information to know where they should stop for food.

- Nanostructuring determines the shape of the patterns and the colors on butterfly wings, which are important for recognition and mating.
  - Coloration comes from a variety of different effects, such as interference, diffraction, and scattering.

  - The colors on most butterfly wings come from thin-film interference, where the coloration is due to alternating layers of high– and low–refractive index materials. The patterns that are used to generate the interference and produce the colors we see originate at the nanoscale.

Natural Nanomachines

- All the energy produced in our bodies is made by a nanoscale machine called ATP synthase. This machine uses hydrogen atoms as fuel and produces a molecule called ATP, which is essential for almost all of the functions of our bodies.
  - The most important component of ATP synthase is a rotating stalk that sits in the membranes of our cells.

  - When a hydrogen atom is taken into the ATP synthase, this causes the stalk to twirl. The protein then uses the energy created by the movement of the stalk to make a molecule of ATP.

- There are also nanomachines in the body that produce all of the proteins needed by cells. This machinery is called the ribosome, and it's a complex of 3 very long RNA molecules and about 75 different proteins. It measures about 30 nanometers, and there are many copies of the ribosome throughout our cells.
  - The ribosome carries out a complex set of steps. It first binds a messenger RNA—a transient copy of a sequence found in the DNA genome. The ribosome then recruits transfer RNAs, which match up with the sequence of the messenger RNA. Each transfer RNA has an amino acid attached.

  - In response to the sequence of the messenger RNA, the transfer RNAs line up, and the ribosome zips together all the amino acids to form a protein, rarely making a mistake.

- Another impressive natural nanomachine is made possible by a substance called actin, a protein that polymerizes and can form extended structures. Actin forms a nanomachine with another protein, myosin, that gives our muscles the ability to move us around.
    - Myosin harvests energy from ATP to propel itself along actin filaments; this is how we get movement at the nanoscale.

    - This movement is translated to movement at the macroscale through the action of billions of myosin molecules consuming billions of ATP molecules in our muscles.

Functionality in Manmade Nanomachines

- Have we been able to reproduce artificially the functions of these kinds of natural nanomachines? We haven't even come close. As you saw at the beginning of the lecture, we've really only been able to make machines that can move around in simplistic ways. We have not yet created a machine that could actually make a product like the ones made by natural nanomachines.

- On the other hand, our ability to understand and use the astonishing nanomachines provided by nature is getting better and better. It may be that our best bet when it comes to making nanomachines is to take what nature has come up with and figure out how to control it using the tools of nanotechnology.

Suggested Reading

Jones, *Soft Machines*.

Mallouk and Sen, "How to Build Nanotech Motors."

Williams and Adams, *Nanotechnology Demystified*.

Questions to Consider

1. What would motivate living organisms to manufacture and use nanomaterials?

2. Are nanomaterials and nanotechnology-enabled products inherently high in cost? If not, what drives some to be low and others to be high?

On the Horizon and in the Far Future

Lecture 24

In this, our final lecture on nanotechnology, we look at some exciting topics that are a little less explored than those we've covered throughout the course. To conclude our course, we'll look at Richard Feynman's predictions about what we might find at "the bottom" and think about what the future might bring.

Smart Dust

- The term "smart dust" is used to describe the idea of having sensors everywhere that could measure properties in our environment. This would be useful for military applications, in which we would like to be able to send tetherless sensors into an environment for monitoring purposes.

- We have all the building blocks already to create such small, ubiquitous sensing devices, but there's an integration problem: putting together the storage of energy. For such a system, we would want to harvest energy from the environment. We might do so photovoltaically or by scavenging energy.

- A further challenge is presented by networking. When we launch these sensors into a region, how can we ensure that they all communicate back to some kind of base station? It might be possible to form ad hoc networks; these would allow the smart dust motes to talk with one another and gradually relay the information back to a central point. There are also small smart networks that can figure out how to form and propagate information in an energy-efficient manner.

- As mentioned, smart dust would be useful for military applications and environmental sensing. Another application might be found in the smart grid. One of the key components of a smart electrical grid would be effective sensing of the electrical properties of the

power that is conveyed or delivered to the grid, combined with management of energy across the grid.

The Cloak of Invisibility

- The idea of a cloak of invisibility is to wrap an object in a material that essentially ensures that electromagnetic waves, such as light or microwaves, will pass around it and recombine as if the object was not present.

- Normally, an object alters light impinging on it or microwave-frequency radiation impinging on it both at the source and in transmission on the far side of the object. The object alters what happens to the wave fronts. Instead of being planar and flat, they become rippled. When they're interfered with in this fashion, the waves render the object causing the interference detectable.

- To make something truly invisible, we would need the optical wavelengths to manifest a property of not being disrupted by the object. We would also need to ensure that there's no absorption. Metamaterials have made progress in this direction.

- Metamaterials are artificial materials, in which pure phases of one crystal, metal, semiconductor, or other material are combined in a periodic or partially periodic structure such that they influence the dispersion of electromagnetic waves.

- These metamaterials were initially implemented at microwave frequencies, but there has been recent progress in building and using them at optical length scales. There are, however, two challenges that remain unresolved.

    - First, the way these dispersion properties are engineered means that we can mostly achieve cloaking only in a single frequency. Cloaking something across the full visible spectrum will be much more challenging.

- Second, there is still some absorption of light that occurs within these metamaterials, which means that they remain detectable, for the moment.

Conformable and Deformable Nanomaterials

- We've talked in this course about numerous subjects: the capabilities of semiconductors, such as silicon, in electronics; the fact that gallium arsenide is a good material for light emission and for making solar cells; single-walled and multi-walled carbon nanotubes that can be coated onto substrates; and quantum dots.

- We've also noted that in working with these materials, we're often interested in integrating multiple functions. We might like to put down an electronic device on silicon, combine it with an energy-harvesting device based on gallium arsenide, and perhaps add a photodetector made out of a third material.

- Traditionally, semiconductor processing and growth have worked based on a process known as epitaxy, the growth of perfectly lattice-matched crystals on top of one another. But some of the materials we've discussed don't even necessarily have lattices; they could be amorphous, or crystalline, or have non-planar shapes. Thus, it's not obvious how we can use our traditional stack of crystals to build stacked heterostructures.

- John Rogers, a professor at the University of Illinois at Urbana-Champaign, has made incredible strides in this area. He has developed ways to put down a diverse array of materials on a template and then use a transfer printing process to transfer this layer onto another substrate. The ability to combine rigid and flexible materials Rogers has achieved in this way is quite powerful.
  - This innovation has allowed us to combine devices that look in different frequency regimes. We can, for example, take the building blocks of radio-frequency electronics—the basis for our cell phones—and combine them with materials that are suited to imaging in the optical domain.

- Rogers's work is also enabling devices that allow cardiac mapping by integrating electronics and biological materials. This could lead to implantable electronic materials that could be used in medical applications.

- The integration of rigid and flexible substrates also shows promise for reducing the cost of devices used for solar energy harvesting.

- Another interesting application for conformable materials that have a shape memory is in the introduction of cardiovascular stents. These could be engineered to have a condensed phase to enable insertion and an expanded phase for function once they are in place.

Environmental Risks

- Many researchers are exploring the consequences of either deliberate or accidental introduction of nanoparticles into the environment. Certain nanomaterials are broken down in the environment in the same way as organic molecules. Others are retained for longer periods of time and have the potential to be taken up as part of an ecosystem and do damage.

- From a regulatory and environmental standpoint, the issues that are presented through nanotechnology are not qualitatively different from the issues that exist across processed chemistry. Like all fields involved in the synthesis of new materials or structures, it's important for nanotechnology to be part of the regulatory process and to be aware of the health implications of new materials.

Richard Feynman's Predictions

- In 1959, Richard Feynman issued an invitation to enter a new field of physics with his speech "There's Plenty of Room at the Bottom." Feynman did not believe that the regime of the very small would further illuminate fundamental physics but that it would provoke great interest in what happens when phenomena are combined in complex fashion.

- At the time that Feynman was speaking, the transmission electron microscope was available, and researchers were imaging natural materials on the length scales that we have discussed. Feynman wondered how we could turn this capability around and start to engineer on these length scales ourselves. He pointed out that it was not beyond our capabilities to imagine writing the 24 volumes of the *Encyclopedia Britannica* on the head of a pin.

- Feynman asked: Why not transform our electron microscopes from readers to writers? Let's orient our atomic beams and carve matter, change the properties of materials. Interestingly, electron beam lithography is one of the major ways of crafting matter at the nanoscale.

- Feynman also pointed out that DNA already showcased the ability to write the *Encyclopedia Britannica* on the head of a pin. In that sense, he anticipated that nanotechnology would get inspiration from biology.

- Although Feynman said that there's plenty of room at the bottom, he was taking a top-down view. Further, he didn't anticipate the crucial role the field of electronics would play in the exploration of the bottom, and he didn't touch on the ways in which the rules of physics are altered at smaller length scales.

- Feynman noted that the capability to work on smaller length scales would have significant technological implications, but he didn't speculate about what they would be. Such applications are hard to anticipate because they are often driven by the needs of people and society.

- Just as Feynman wasn't able to anticipate all the areas of application, we, too, have just scratched the surface of the implications and applications of working with materials at the nanoscale. We invite you to stay tuned to this field as it evolves and we witness remarkable developments in the future.

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Wikipedia, "Metamaterial."

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Questions to Consider

1. How could smart dust be deployed for (1) peaceful environmental and/or water quality monitoring purposes and (2) military purposes?

2. If a company or a country wanted to gain a distinctive place as a leader in nanotechnology, what would it have to do to secure such a competitive advantage?

3. Which of the ethical and societal issues that nanotechnology raises are nano-specific? Which are shared with any new technology? In light of the potential rewards and risks—foreseeable and unforeseeable—of nanotechnology, should it be pursued and, if so, how?

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